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Original Communications*

THE PATHOLOGIC DIAGNOSIS OF EARLY CERVICAL AND CORPOREAL CANCER WITH SPECIAL REFERENCE TO THE DIFFERENTIATION FROM PSEUDOMALIGNANT INFLAMMATORY LESIONS

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IN A RECENT paper[1] before the Southern Surgical Association, I discussed the importance of biopsy and diagnostic curettage in the recognition of early uterine cancer, and urged that the prevalent conception as to the pathology of uterine cancer needs freshening. The physician who in his mind associates this disease with a cauliflower growth of the cervix, or with a foul, excavated crater ulcer, is apt to feel relieved if his examination of the patient with a suspicious history shows no such lesions. And yet, in just such cases, the cervix may furnish perfectly valid, though not so obvious, evidence to warrant the diagnosis, or at least the strong suspicion, of malignancy.

It is these earlier pictures of malignancy, therefore, with which the profession should learn to familiarize themselves, for it is from this early group that we can hope to garner a considerable proportion of cures. A fair analogy may be drawn with the changed concept as to the clinical picture of other diseases, such as appendicitis. One no longer withholds his diagnosis until, as was at one time the case, the patient exhibits abdominal distension, persistent vomiting, profound prostration, a hippocratic facies, and other evidences of a peritonitic sequel of the original disease. Similar comparisons might be made with other conditions.

*All of the papers included in this issue of the Journal were read at the Fifty-fourth Annual Meeting of the American Gynecological Society, Old Point Comfort, Va., May 22-24, 1929. The remaining papers and discussions will be printed in the November issue.

There can be no doubt that the educational campaign against cancer is bringing an increasing number of cases to the physician in an early, favorable stage of the disease. The physician must be prepared to do his part by recognizing suspicious lesions, and by seeing that each patient's individual problem is authoritatively settled, as, with rare exceptions, it can be. It is the gynecologist who will be called upon for this responsible task, which he must undertake either alone or with the collaboration of a skilled pathologist.

More and more, as cases come earlier, the microscope will be called upon to make, rather than merely to confirm, the diagnosis of uterine cancer. Difficulties in the diagnosis of late cancer are as rare from the pathologic as from the clinical standpoint. When dealing with early lesions, those which clinically are usually only suspicious of cancer, the microscopic interpretation is not always so easy, although, with comparatively few exceptions, the well-equipped pathologist can decide the question correctly.

The microscopic characteristics of cancer in the outspoken case are so clearly defined that the diagnosis is a purely objective one, in which all pathologists agree. With a certain group of borderline cases, on the other hand, it is hard to keep out the subjective factor, for pathologists will differ in their interpretations as to what constitutes good microscopic evidence of beginning malignant transgression of epithelial tissue. The term borderline, in this connection, is used from the standpoint of interpretation and not to indicate that one is actually dealing with an intermediate stage between benign and malignant disease.

In my previous paper, already referred to, I stressed the fact that, because of the rather specialized physiologic and pathologic variations in structure encountered in the uterine mucosa, the gynecologic pathologist, who has daily opportunities of studying such lesions, has some advantage over the general pathologist. To put it another way, a man may be an excellent general pathologist, in the ordinary sense of the term, and yet go wrong rather easily in the interpretation of many of the lesions of the genital organs.

It is scarcely necessary here to elaborate upon the pathologic criteria of malignancy in general. From the standpoint of microscopic examination, they fall into two groups, viz.:

(a) *The General Pattern.*—The general impression which is given by the low-power examination suffices to make the diagnosis in most cases of cancer, but this, on the other hand, may not be conclusive in the early or doubtful case, as will be discussed later. Under this head comes also the question of the invasiveness or noninvasiveness of the epithelial growth, which, in the borderline case, may not be of much assistance in making the diagnosis. For that matter it is not uncommon in many sections of undoubted cancer, particularly with adenocarcinoma of the uterus, to observe no evidence of penetration of the basement membrane, or invasion of the underlying tissue. In the lat-

ter sense there is commonly far more invasiveness to be seen in the perfectly benign adenomyoma. Finally, in making diagnoses from uterine scrapings, in which one has to deal with fragments of mucosa alone, one can expect little help in deciding as to whether or not the disease is invasive of the musculature.

(b) *Atypical Characters of the Epithelial Cells.*—In the more obvious stages of cancer, the high power picture is apt to be studied chiefly to confirm the impression of malignancy already obtained from the low power survey. When the latter is inconclusive, however, as it is apt to be in the early or borderline cases, one must concentrate, in a very analytic way, upon the finer study of the cell characteristics. Lack of differentiation of the cells as compared with the normal prototype, and such nuclear abnormalities as mitoses and hyperchromatosis are especially important. In the nonmalignant hyperplasias such changes are not in evidence, although misleading pictures may be encountered. For example, as I shall discuss later in this paper, one may find heavily stained nuclei and perhaps even an occasional mitosis in certain inflammatory lesions of the cervix which are definitely benign.

THE DIFFERENTIATION OF CERVICAL LESIONS

It is in the cervix that one most often encounters pictures calling for careful differentiation. Certain benign lesions, especially those of inflammatory character, not infrequently give rise to gross appearances which suggest malignancy so strongly that no clinician should be willing to assume the responsibility of making the decision without the aid of the microscope. This is particularly true of cervical polypi and chronic endocervicitis, especially when in association with either erosion or ectropion. The latter is, of course, most often seen with lacerations. In cases of this sort, the everted mucosa is not infrequently red and granular, and perhaps bleeds on slight touch. (Fig. 1.) Moreover, it may show a definitely papillary or sprout-like tendency, and, on palpation, may give a sense of definite induration.

Clinically, such lesions belong in the category labelled suspicious, and I know of no other way in which the decision can be made than by biopsy and microscopic examination. For a discussion of this procedure I would refer to my previous paper, in which I have also discussed the question of the alleged danger of disseminating cancer cells by biopsy, or by diagnostic curettage.

The evidence for such a danger is far from convincing, but even if there were some danger, it would be far less, in my judgment, than to leave the issue in the individual case undecided or decided wrongly. How else can the decision be made in these clinically doubtful cases than by means of biopsy? To treat such cases conservatively would probably spell death to the patient if the lesion be actually malignant. On the other hand, to decide that radical treatment is advisable because

the lesion, if not cancerous, is at any rate "precancerous," is slipshod and unscientific. It may entail for a lesion that is perfectly benign an unnecessary and more or less dangerous operation, or unnecessary and more or less distressing radium therapy.

The microscope will settle the question in all but a very small proportion of cases. A good frozen section will usually suffice, for cervical biopsy tissue is well adapted for frozen section work. If there is any doubt, good sections by the permanent technic are of course desirable before deciding on the plan of treatment.

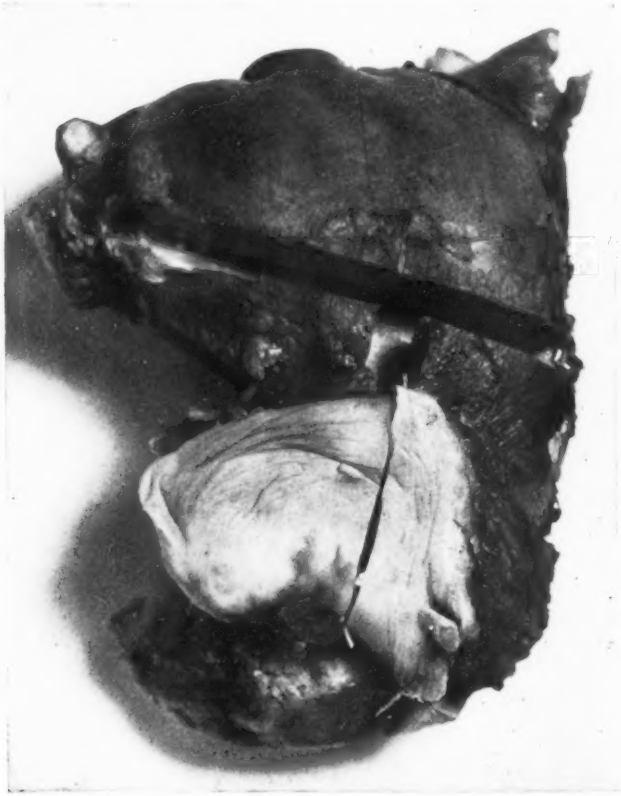

Fig. 1.—A lesion of the cervix which clinically was strongly suspicious, and in which biopsy showed the cancer depicted in Fig. 7. Panhysterectomy and double salpingo-oophorectomy were done (the adnexa were cut away in order to search for ova in the tubes).

From a microscopic standpoint, inflammatory lesions of the cervix may be confused with either squamous cell carcinoma or adenocarcinoma, though more frequently with the former. The reason for this is that chronic inflammation not only leads to the so-called "epidermization" of the cylindric epithelium, but excites the squamous epithelium, normally limited to the surface, to an invasion of the stroma. A section of such a cervix will often, therefore, reveal cell nests and

columns of squamous epithelium in the depths of the stroma, producing a picture not unlike that seen with squamous cell carcinoma. Many mistakes in diagnosis have been made because of this, but error can be avoided if one understands the mechanism, characteristics and significance of this invasion of epithelium. For the elucidation of this we are indebted chiefly to the investigations of Meyer,[2] although such pictures had been described by Ruge,[3] and many others, before him.

For a proper understanding of this question, it is necessary to bear in mind the development of the epithelial lining of the uterine and cervical canals. All of the genital epithelium, with the exception of

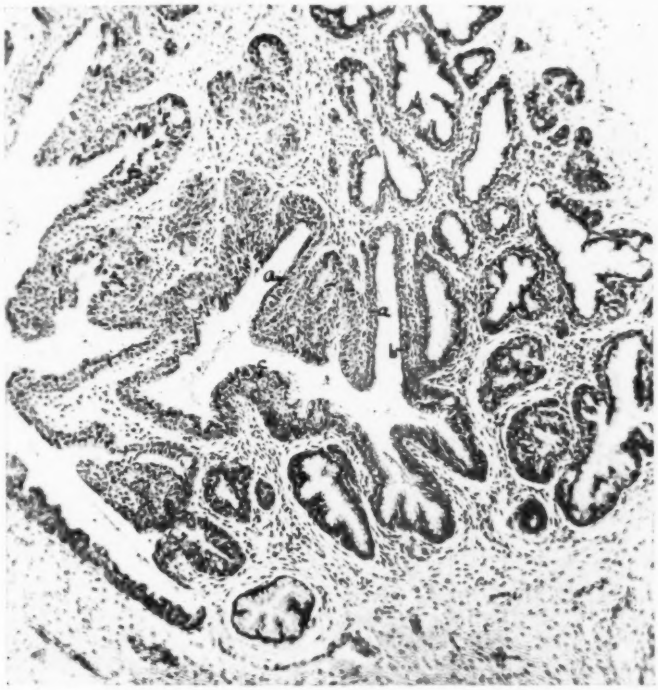

Fig. 2.—Showing manner in which creepers of the basal layer of stratified squamous epithelium push beneath the cylindric epithelium (*a*). In other places (*c*) there are several layers of stratified epithelium beneath the cylindric, and the cells of the latter are becoming flattened (*b*) or degenerated (*c*). A high power picture of the same field is shown in Fig. 3.

that covering the lower portion of the vagina, is ultimately derived from the same mother tissue, i.e., the celomic epithelium. By the third or fourth month of fetal life the differentiation between the cylindric epithelium of the uterine canal and the squamous epithelium of the pars vaginalis is quite distinct. It is important to note, too, that the line of transition between the two types is not at the exernal os, but well within the cervical canal. This is due to the manner of formation of the vaginal fornices, which are developed in the zone of squamous epithelium.

At a later stage, put by Meyer at about the sixth or seventh fetal month, the secretory activity of the cylindric epithelium becomes manifest. The destructive effect of the secretion pushes the squamous epithelium out to the region of the external os. Often, indeed, it is crowded even further out, so that cylindric epithelium covers an areola of variable size about the os. Thus is produced the so-called congenital erosion.

The explanation which Ruge gives of this epithelial interplay, and of the formation of congenital erosions, differs from that of Meyer, but I believe the latter to be the correct one. It is not easy, however, to understand how the mucinous secretion of the cylindric epithelium exerts such a destructive effect upon the squamous epithelium, and it

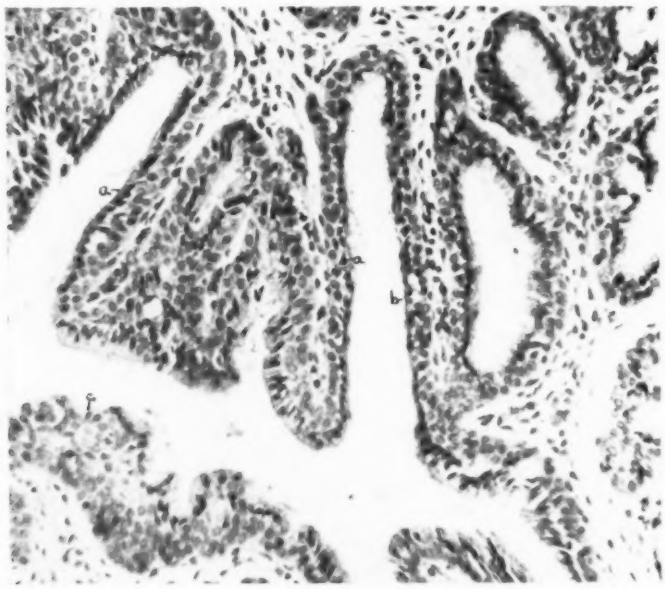

Fig. 3.—High power of areas represented in Fig. 2.

seems possible that some other factor, as yet unknown, may be more important.

The same interplay of the two types of epithelium is seen in later life, under the influence of inflammatory irritation. As a first stage in endocervicitis there is produced a hypersecretion of the cylindric epithelium and an extension outward to the pars vaginalis, with the production of an erosion. In this stage, which Meyer calls the first healing stage, the erosion is covered with a cylindric epithelium. The latter still retains its gland-forming tendency, so that new gland invaginations may be formed far out on the pars vaginalis. As the inflammation recedes, the squamous epithelium again asserts itself, pushing back the cylindric epithelium to the region of the external os.

It is during this, the second healing stage, that one observes the squamous cell invasion below the surface with which we are especially concerned in the differentiation from cancer. Long tongues of squamous epithelium creep along the basement membrane, lifting and often destroying the cylindric epithelium (Figs. 2, 3, and 4). It is common to see this invasion beneath the gland epithelium. Often, instead of a stratified squamous epithelium, one sees only the basal layer of the latter creeping along beneath the gland epithelium, giving an appearance of stratification to the latter (Figs. 2, 3, and 4). As the process advances, the entire gland lumen may be filled with the stratified squamous epithelium, and the cylindric epithelium, as it were, choked

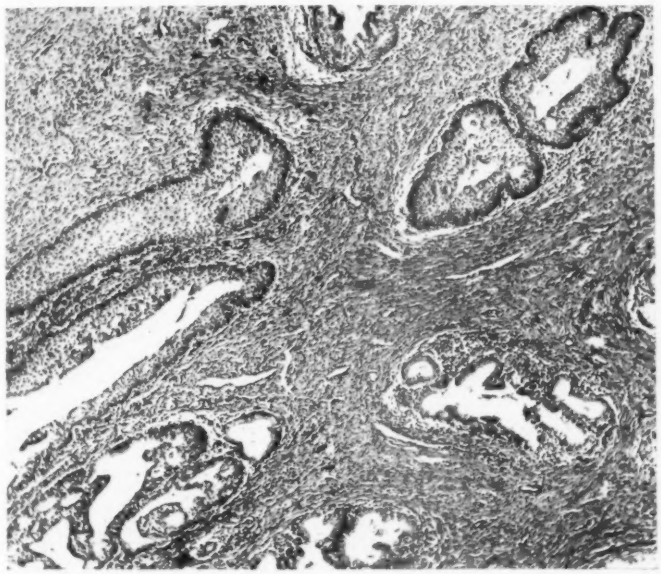

Fig. 4.—Showing, above and to left, a nest of epithelial cells resulting from an advance of process described in Fig. 2, the gland lumen being entirely filled, and the columnar epithelium being choked off. The gland below this, and also the one to the right, show a less advanced stage of the same process, with some of the columnar cells still persisting. In lower left-hand corner is a fenestrated gland picture, produced by a combination of the same change with the adenomatous reduplication of the cylindric epithelium often seen in inflammatory lesions. No evidence of malignancy in any of these areas (see text).

to death (Fig. 5). In the latter case, the plugs of squamous epithelium often exhibit small central gland-like cavities filled with mucinous substance, as can be demonstrated by differential staining. In less extreme areas, the cylindric epithelium may still be demonstrable.

Such pictures may lead to a strong suspicion of adenocarcinoma, and I know of several instances in which the mistake has been made. The changes which have been described may in long-standing cases alternate repeatedly, and different phases may be observed in different parts of the cervix at one and the same time.

From what has been said, it will be seen that this invasion of the depths by creepers of squamous epithelium takes place characteristically on the trellis furnished by the gland framework (Fig. 4). This, as Meyer emphasizes, is one of the most important points in the differentiation from cancer. The penetration of actual cancer may of course involve the glands also, but this invasion is a more ruthless and less orderly one, and is not of course confined to the gland elements, as with the inflammatory process just described (Fig. 6). With the latter, the surface epithelium is normal, or at any rate, shows no sign of malignancy. With cancer the surface epithelium is usually distinctly atypical, and frequently has been lost by ulceration. In the

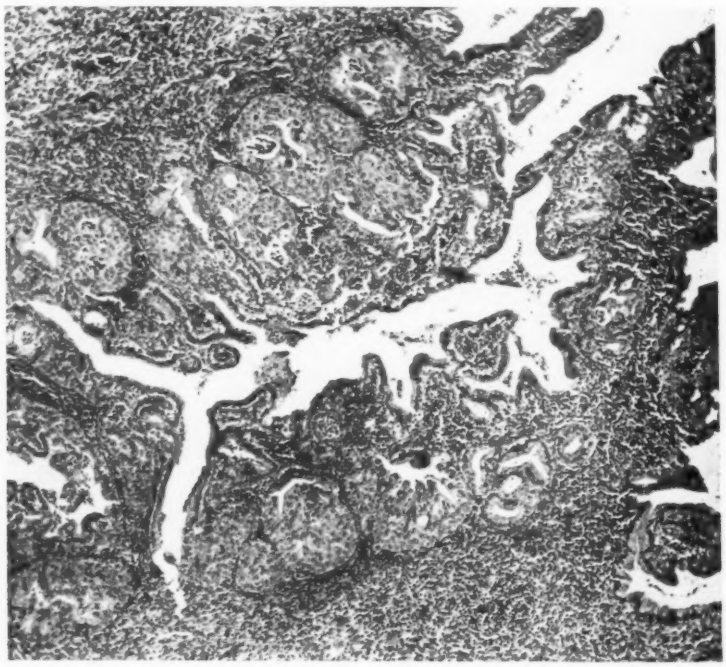

Fig. 5.—Pictures like this, not uncommon, might readily be mistaken for cancer. The patient was twenty-six years old, and has remained perfectly well after simple excision of the cervical polyp from which this was taken. The cell nests beneath the columnar epithelium are due to the same benign extension of the squamous epithelium depicted in the preceding pictures. The constituent cells show none of the characteristics of cancer cells. The overlying columnar epithelium is likewise normal, except for some flattening and degeneration.

cancerous process, nests of atypical epithelium are to be seen invading the stroma everywhere, and, except in the earliest stages, usually more extensively than one sees in the inflammatory process. In the latter, it is true that in individual sections many of the nests appear to be quite independent of the gland structure, but, with some exceptions, serial section study will show that this is not the case. A study of the invasive process in the glands themselves shows how easily one may be misled by the angle of section.

It should be added that the above explanation of this process, as championed by Meyer, and with which my own observations lead me to agree, is not the only one which has been suggested. There are still some who believe that there is, in these cases, a genuine metaplasia of the cylindric to the squamous type of epithelium. The chief support for this, it seems to me, would come from the not infrequent finding of squamous epithelium in gland epithelium far removed from the surface, and showing no connection with the latter even by outriders of the basal layer of the squamous epithelium.

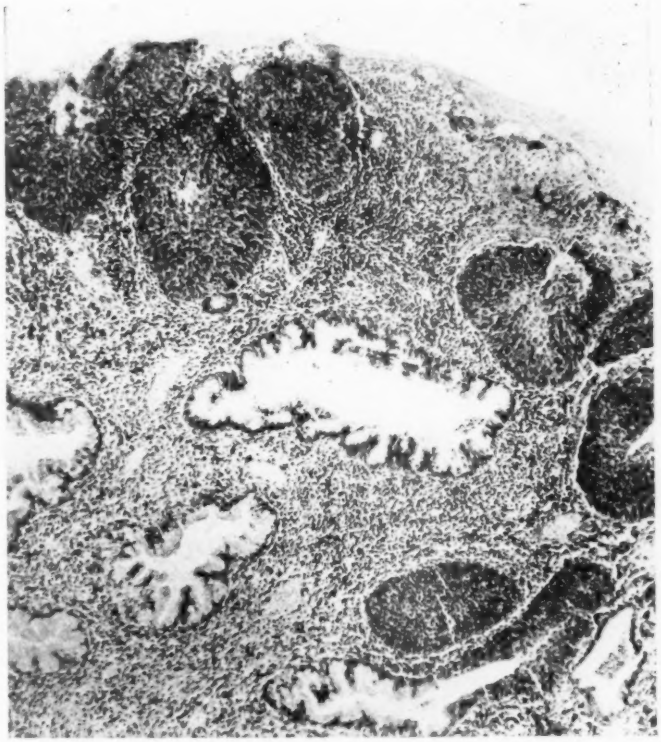

Fig. 6.—Early squamous cell cancer in a patient with only suspicious cervical lesion in which no biopsy was done. The diagnosis was made after and not before the operation, as might have been done. Note the difference between these cell nests and those shown in Fig. 2. Under the high power the cells are seen to be closely packed, placed chiefly like palisades perpendicularly to the basement membrane, and showing the usual cancer characters (mitoses, hyperchromatosis, etc.). The cell nests here are independent of the glands, although of course glands are often invaded in cancer also.

Such pictures Meyer would explain on the ground that, with the interplay of epithelium produced by inflammatory disease, rests of squamous epithelium are left stranded, so to speak, beneath the cylindric epithelium, developing active growth later on. Although he has demonstrated islands of cells which he interprets in this way, it seems to me that the evidence on this point is somewhat less convincing than that bearing on other features of the general process. In spite of

Meyer's emphatic declaration to the contrary, I am inclined to believe, with Ruge, that in the cervix, as in the body of the uterus, genuine metaplasia of cylindric to stratified squamous epithelium may at times occur, though not vice versa. Moreover, pictures are at times observed which suggest that there is a marked dipping in of the squamous epithelium independent of the gland invaginations, and suggesting a benign prototype of the scharlach-R cancer described by Fischer.

After all, however, the differentiation of these inflammatory lesions from very early cancer is based upon the study of the cells themselves

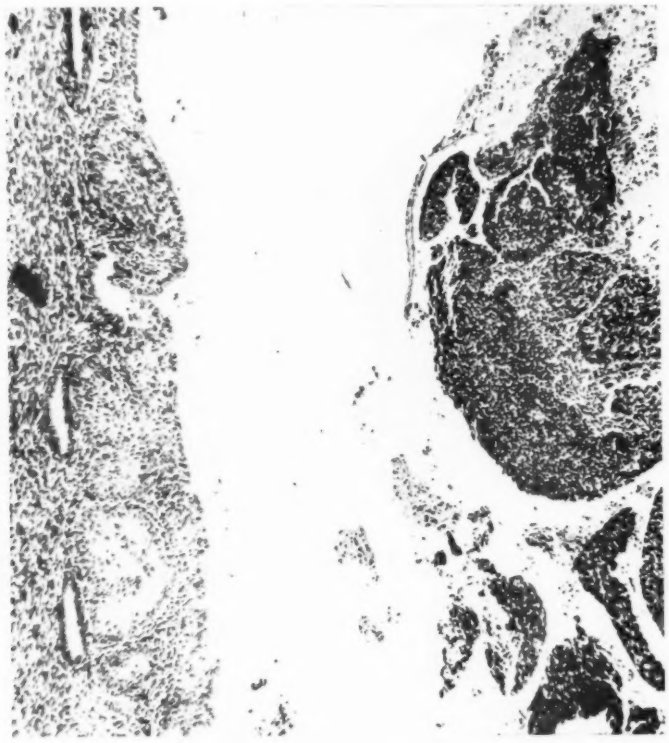

Fig. 7.—Section from uterus represented in Fig. 1, showing benign inflammatory "metaplasia" on one lip (left) and definite cancer on the other (right).

rather than upon such differences in general architecture as have been discussed (Fig. 7). In the diagnosis of cancer beyond the earliest stages, of course, the general pattern suffices to make the diagnosis for the trained microscopist. A glance through the low power lens is often all that is needed, the high power being used merely for confirmation and finer study. When dealing with very early and doubtful cases, however, every possible resource must be made use of, and even then there will remain a small residuum of cases in which a positive diagnosis cannot be made.

Even though numerous cell nests are found in the stroma, cancer would hardly be thought of if these cells show a perfectly typical structure, i.e., if they are of uniform nuclei, and with no evidence of mitoses, hyperchromatosis, and other nuclear changes suggestive of malignancy. Another point of differentiation is the fact that in the benign lesion it is only the basal cells of the epithelium which are arranged perpendicularly to the basement membrane, like palisades; while in cancer this perpendicularity is often noted in the upper layers as well. In the majority of instances the diagnosis is easy, especially when based upon a thorough study of the entire section, or preferably of a number of sections. The clinical history, especially as to the age of the patient, the gross appearance of the lesion, and the presence or absence of bleeding, are of great auxiliary importance, and certainly the pathologist is entitled to all such data when asked to pass upon the question of malignancy or nonmalignancy.

In a small proportion of cases the epithelial cells of the surface, or those in cell nests beneath the surface, present an intermediate sort of picture which makes the decision extremely difficult or perhaps impossible. The stratification of the epithelium of the surface may be well preserved, but the cells may be somewhat more compactly packed. The nuclei, especially of the basal layers, may be large and heavily stained, and rarely a few mitoses may be observed. It is of course the basal layer from which regeneration normally takes place, but mitoses are almost never seen in this layer under normal conditions or even in inflammatory lesions. They are even more rare in the superficial layers, and I do not recall ever having seen them in these strata except in malignancy. To deny, however, that in the occasional case, one may find such mild evidences of nuclear activity as above mentioned, even including an occasional mitosis in the deeper layers, would be unjustified.

The same difficulty is encountered at times in inflammatory lesions in interpreting the pictures presented by the cell nests in the stroma. When the section has passed through the basal layers, one may find the same dark, heavily stained nuclei and the same rather compact epithelium above mentioned. Other areas, however, may show a more distinctive picture, and the surface epithelium may be quite normal in appearance. Numerous sections are advisable before arriving at a final diagnosis in this, perhaps the most difficult of all groups.

Just what to do in cases where a definite doubt exists must, I think, depend upon the circumstances of the individual case. If the patient be comparatively young and the gross lesion not especially suspicious, treatment should be expectant, with repetition of the biopsy within a few weeks. If, on the other hand, the lesion be distinctly suspicious, even microscopically, and the patient be of the cancer age, there are many who would feel justified in instituting the usual treatment for

cancer, either radium or surgery, depending on circumstances and predilections. If operation is done, the diagnosis can usually be definitely established from the extirpated uterus, and in a considerable proportion, perhaps the majority, of such cases, malignancy will not be found. With radium, on the other hand, such a check-up is not possible, and hence the accuracy of the pathologic control of such cases is obviously less to that extent. It should again be emphasized, however, that only a small proportion are of this type, i.e., both clinically and pathologically doubtful, and that in the great majority of instances, accurate diagnosis is possible from biopsy sections.

There is one other benign picture which merits mention, because of its great frequency and the fact that it is not so rarely falsely diagnosed as cancer, in this case adenocarcinoma. I refer to the fenestrated, acinous appearance seen so often with inflammatory lesions, and especially in polypi, and which is well shown in Figs. 4 and 5. This picture I believe to be due to two factors. The stratification is unquestionably the result of the aggressive overgrowth of the stratified squamous epithelium which has been described already. There is, however, apparently a genuine increase in the number of gland lumina, which I believe to be due to the adenomatous tendency of the cervical epithelium under the influence of inflammation. In chronic endocervicitis one commonly observes that the epithelium on the surface, instead of being perfectly smooth, exhibits a very wavy outline due to this invaginating tendency. In more marked stages, the adenomatous tendency is undoubted, almost suggesting that so characteristic of the histologically similar lining epithelium of a pseudomucinous cystadenoma of the ovary. The gland-forming tendency is exhibited also by the epithelium lining the glands, so that complicated patterns, like lacework, are often produced. And yet the cylindric epithelium, when not smothered by the squamous, is of one cell thickness, often somewhat flattened, with no suggestion of malignancy.

THE DIFFERENTIATION OF ENDOMETRIAL LESIONS

In cases of uterine bleeding which present no incriminating gross findings or symptomatic features, and especially when the cervix reveals no suggestion of malignancy, diagnostic curettage is of decisive importance in a very large proportion of cases. Not infrequently the gross appearance of the tissue removed by the curette is sufficiently characteristic to permit of reasonably accurate diagnosis. When the curettings are abundant and contain rather large bits of tissue, satisfactory frozen sections can be obtained for diagnosis or confirmation. This will prove to be the case in most cases of cancer, so that, if the naked eye and the microscopic findings both indicate cancer, the surgeon can feel entirely safe in proceeding with radical operation under the same anesthesia. The advantages of this are obvious.

If, however, the curettings are scanty and not characteristic, satisfactory frozen sections are difficult to obtain, and it is wise to wait for fixation of the tissue by one of the permanent technics. In most cases, however, cancer will not be found, so that another anesthetic is not necessary except in the unusual case of very early carcinoma.

From a microscopic standpoint the diagnosis of the great majority of cases of adenocarcinoma of the uterus presents no difficulty. In the early cases it is of importance to examine all the tissue removed, and to make a number of sections at various levels in the block. Otherwise the early, localized lesion may easily be missed.

Inflammatory lesions of the endometrium rarely give rise to pictures which might lead to confusion in the diagnosis, whether or not the cause of the inflammation be a retention of gestation products. In the latter case there are usually telltale bits of evidence in the presence of chorionic villi, decidual cells, etc. With chronic inflammation of marked degree there may be some distortion of glands, but the picture does not in any way suggest malignancy. The interstitial inflammatory process usually dominates the picture, the glands often being pushed apart or distorted because of this. Epithelial changes suggestive of malignancy are absent.

With benign hyperplasia and polypi there is at times some difficulty in making the diagnosis. The very nature of hyperplasia suggests a proliferative activity of the epithelial as well as the stromal elements. A single section may not show the characteristic Swiss-cheese pattern, which would at once give the clue. It may reveal only a mass of rather thickly crowded glands, in some of which the epithelium may be much thickened, with dark heavy-staining nuclei. This is not an uncommon finding, for in some areas of the hyperplastic endometrium the glands may be thickly crowded together. Mitoses may be numerous, although this means very little in a tissue which, because of its cyclical regeneration, shows a greater or less number of mitoses as a normal finding. Pictures like those just described have more than once been wrongly diagnosed as "adenoma malignum." At times, it is difficult to be sure of the diagnosis from the single section, although almost always other sections will reveal a more or less distinctive picture, clearing up the diagnosis satisfactorily. In a small proportion of cases, however, the diagnosis must remain doubtful and a repetition of the curettage is advisable after a few weeks.

There is one other occasional finding which has been much discussed and which may puzzle the microscopist who is not familiar with it. I refer to the so-called "epidermization" of the endometrial epithelium. This squamous cell transformation of the normally cylindric epithelium may be occasionally seen not only in undoubtedly benign lesions, but, in my experience, is much more common in adenocarcinoma of the

body of the uterus. It occurs, too, in adenocarcinoma of the cervix. There can be little doubt that it explains most of the cases which have in past years been reported as instances of combined squamous cell and adenocarcinoma. (Fig. 8.)

The occurrence of "epidermization" in benign lesions of the endometrium is, however, far less frequent. Fluhmann,[4] in a recent study of the literature, was able to collect only 5 cases in addition to his own, but I believe that the occurrence is not quite so rare as these figures

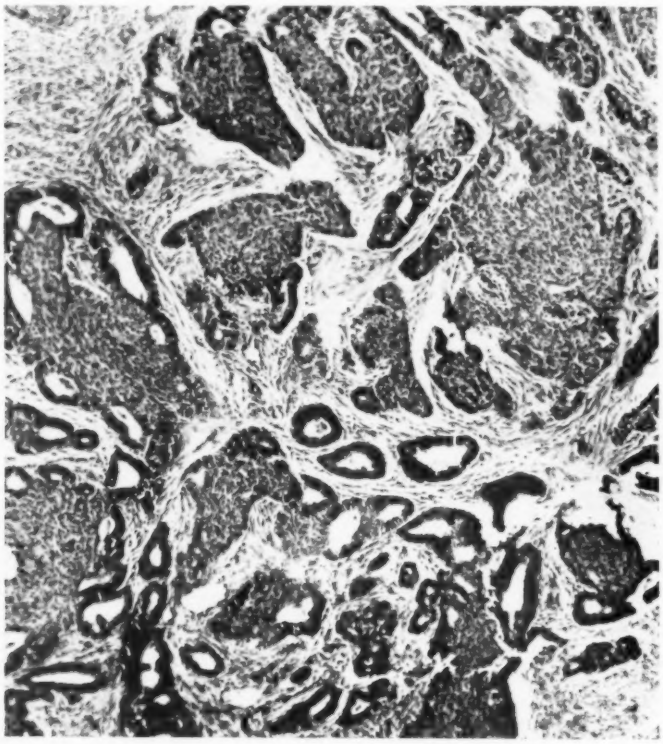

Fig. 8.—Extensive squamous metaplasia in an adenocarcinoma of the uterus. Here there is no doubt of the transition from a primarily gland carcinoma, but in other areas the squamous change is so extensive that the primary character of the tumor is blotted out. Such cases have in the past often been wrongly interpreted as combinations of squamous cell and adenocarcinoma.

would indicate. I have found this picture in several cases, most recently in the one which is illustrated in Figs. 9 and 10. Hintze,[5] in a recent report, described 9 cases encountered in one laboratory within a period of five years, and collected a number of others, some of which had not been included in Fluhmann's collection.

There has been considerable discussion as to the etiology and the significance of this "epidermization," or "epidermoidization," of the endometrium. The view has been held by some that this epithelial change is due to the fact that some of the cells in the regenerative

layer retain their indifferent characteristics, being thus capable of developing into either squamous or cylindric epithelium. Meyer, indeed, has described collections of such cells in the uteri of newborn children. So far as I know, however, they have not been observed in the adult uterus, and they would probably soon be lost as a result of the desquamative changes of menstruation and pregnancy. There can be little doubt, therefore, that the "epidermization" represents a genuine metaplasia of cylindric to squamous epithelium.

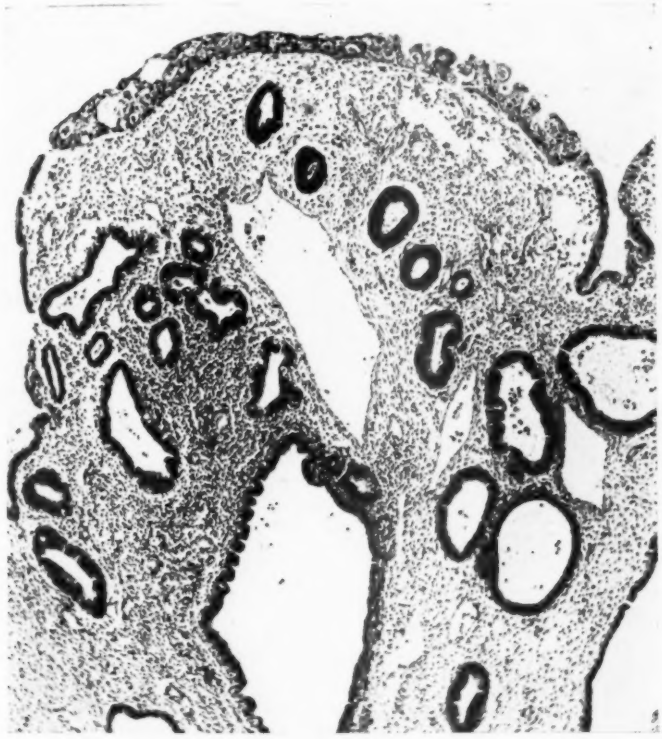

Fig. 9.—Squamous "metaplasia" or "epidermization" of the surface epithelium in a case of hyperplasia of the endometrium and adenomyoma. This is a purely benign change, although in this case a hysterectomy was done for other indications. The patient, aged twenty-three, has remained perfectly well.

As has already been emphasized, the celomic epithelium is the common progenitor of both cylindric and squamous epithelium within the genital canal, and hence it is not surprising that a certain degree of interchangeability of such tissues persists, capable of exaggeration under certain conditions. The strongly proliferative tendency characteristic of hyperplasia, and, of course, even more of cancer, would seem to explain the fact that it is in these two conditions that the metaplasia is observed almost exclusively. A similar epithelial change, however, was described by Mainzer following formalin vaporization of the

uterine cavity, and has been noted also in gonorrheal and other forms of endometritis (Wertheim and Menge), endometrial tuberculosis (von Franque and others). Such a metaplasia, too, was produced by various irritants in the bladders of rabbits (Lubarsch) as well as in the stomachs of the same animals (Fütterer). Oeri, again, speaks of squamous and even cornified epithelial areas in the mucosa of nasal polypi; and also in the mucosa of the larynx, trachea and bronchi. The process has also been noted in the mucosa of the gall bladder, and has been recently described in the ducts of the pancreas. There is nothing surprising, therefore, in the occurrence of such squamous metaplasia in

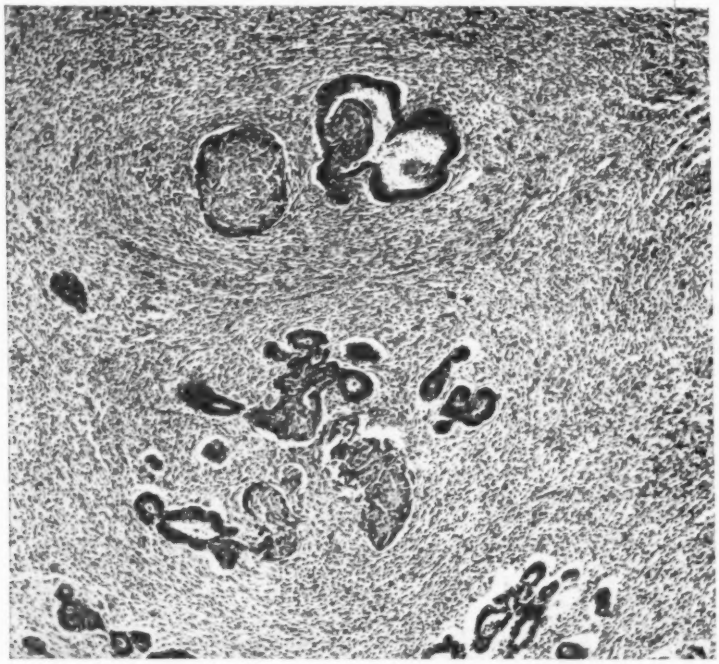

Fig. 10.—"Epidermization" of deeper lying gland epithelium of adenomyoma in same case. These changes, formerly considered as evidence of malignancy, are now looked upon as definitely benign (see text).

the endometrium, where, as a matter of fact, the kinship of the two types of epithelium is closer than elsewhere.

While many of the early writers looked upon "epidermization" as indicative of malignancy, the evidence is now quite convincing that in itself it is an essentially benign process. For example, the endometrium pictured in Figs. 9 and 10 was derived from a patient aged twenty-three, with no evidence of malignancy, although a hysterectomy was done for other indications. Of Hintze's 9 cases, simple curetting was done in all but 2, but all had remained well at periods of from two to five years after operations.

GENERAL CONSIDERATIONS

From what has been said I believe that the emphasis which I have placed upon a really authoritative pathologic examination has been justified. Unless the one called upon to make these diagnoses is not only a competent general pathologist, but is also familiar with such rather specialized pictures as we have been considering, grave mistakes will be made, as they have often been made in the past. On the other hand, the clinician, aside from his general responsibility in the individual case, must not only recognize when the help of the pathologist is needed, but must collaborate with him by supplying tissue from which a diagnosis can really be made.

The tissue in biopsy can be removed by means of a sharp knife, after which the edges of the wound are seared with the cautery. Removal with the cautery knife alone is not so satisfactory, as the small bit of tissue is thereby cooked and shriveled, rendering it valueless for microscopic examination. At times the knife may prove a rather awkward instrument for biopsy, especially when the vagina is deep and when the cervix tends to slip away from the scalpel. In such cases a very useful and convenient instrument is a punch devised for this purpose. It will permit of the rapid biting out of small oval bits of tissue.

Two extra precautions should be urged in the performance of biopsy. First, the excision should be made from the area, perhaps very small, which is most under suspicion, for adjoining parts, in an early cancer, will probably show no evidence of the disease. Second, care should be taken to have the tissue cut at the proper angle in the making of the sections, especially, of course, with a view to showing the mucosa. Where the laboratory man is ignorant of just what the clinician is driving at, and even more in hospitals where the sections are prepared by lay technicians, the section is apt to be cut in such a way as perhaps to show mostly fibrous tissue, with little or none of the mucosa. Negative reports on such sections would, of course, be worse than useless. My own custom is to place the excised tissue on a piece of gauze in exactly the position in which it ought to be cut by the person who is to make the sections. More than one section, moreover, is always desirable, although not always essential for diagnosis.

As I mentioned in my previous paper, the ideal condition of affairs is for the gynecologist to be equipped to make his own microscopic examinations. Such an equipment, not difficult of acquirement to anyone having a ground knowledge of general pathology, is possessed by a certain proportion of gynecologists, but the proportion should be larger. Many otherwise excellent hospital services in gynecology are weakened, it seems to me, by the insufficient stress put upon pathology. Not only is a thorough knowledge of pathology of immediate diagnostic value in such problems as the one we are discussing, but it

broadens and clarifies one's viewpoint on the clinical problems of our specialty as well. No better advice can be given to the young man contemplating a gynecologic career than to become thoroughly and broadly conversant with the pathology of the lesions which he will be called upon to treat. Once such an interest in gynecologic pathology is developed, it will rarely be lost.

The question may fairly be asked, "Are the results of microscopic examination from biopsy and diagnostic curettage sufficiently trustworthy to be used as a guide in the treatment of suspicious cases?" When these studies are made in the manner above outlined I believe that this question can be unhesitatingly answered in the affirmative. The proof of the matter lies, of course, in the subsequent course of cases diagnosed and treated according to this policy. As we have not as yet made a follow-up analysis of our cases, from this standpoint, I can for the present give only impressions rather than actual facts. I cannot recall any case in which a definite diagnosis of malignancy was made from biopsy sections or curettings in which the diagnosis was not confirmed by the examination of the extirpated uterus, when surgery was done. This, of course, does not include a certain number of cases which microscopically were considered only suspicious or doubtful but in which, for one reason or another, a radical operation was done. Nor would it apply to the rare cases, of which I have personally observed none, of adenocarcinoma of the uterus so localized that the lesion was apparently entirely cleared away by curetting. In these, of which a considerable number (between 30 and 40) have been reported, the curettings show definite cancer, while no evidence of malignancy is found in the uterus after extirpation. As hysterectomy is the proper procedure in such cases, anyhow, the value of the preliminary diagnostic curettage in revealing cancer this early is all the more evident.

Several instructive follow-up studies have been made by others which justify the confidence which most of us place in the microscopic examination of doubtful cases. Hirschberg,[6] in 1925, reported upon the subsequent course of 116 cases in which biopsy had been done, and 244 in which diagnostic curettage had been performed. In these groups are included 7 cases in which the diagnostic procedure showed the incorrectness of a more or less definite clinical diagnosis, viz.: 3 biopsies revealing no malignancy where cancer of the cervix had been diagnosed, and 4 curettings revealing a benign lesion of the endometrium when a more or less definite diagnosis had been made of cancer. Of 107 biopsies upon suspicious lesions of the cervix, 30 led to the histologic diagnosis of cancer, 77 to that of benign conditions. These figures, it seems to me, indicate the diagnostic indispensability of these two procedures in the differentiation of suspicious lesions of either the cervix or body.

Perhaps even more impressive are the results of the follow-up study reported by Meyer and Kaufmann.[7] The biopsy cases numbered 165, of which 146 were clinically suspicious of cancer. Twenty-six of these actually were demonstrated to be histologically cancer, the remainder, 117 cases, being diagnosed as benign inflammatory lesions. Among this histologically benign group were 15 cases which had been considered so definitely cancerous from the clinical viewpoint that the biopsy was repeated once or twice, but with the same result. The remaining 3 of the 146 cases permitted of no diagnosis, because of insufficient or unsatisfactory tissue. On the other side of the picture, 2 cases of definite histologic cancer were revealed in which there was no clinical suspicion of cancer.

The cases of diagnostic curettage, 273 in number, were studied in the same manner. Two hundred and sixty of these were clinically classed as suspicious. Of these 29 proved to be cancerous, 223 benign, and 8 showed insufficient tissue for diagnosis. Moreover, 9 cases of definite cancer were unearthed by curetting and microscopic examination, in which there had been no clinical suspicion of cancer, while 3 cases with a definite clinical diagnosis proved to be benign.

After all, the question of whether a lesion is malignant or benign is determined, as Meyer emphasizes, by its effect upon the patient, i.e., by its subsequent clinical course. With this point in view, a considerable number of cases were studied, by Meyer and Kaufmann, in which biopsy or curetting had been done, and which were traced, where possible, and reexamined. Of 43 cases with a clinical diagnosis of carcinoma, but in which biopsy showed no cancer, all had remained perfectly well after conservative treatment. In the same way, in 107 cases in which diagnosis had been made by microscopic examination of curettings, in not one did the subsequent course belie the histologic diagnosis. This, of course, is a remarkable record, possible only where the clinical and pathologic studies are well coordinated, and where the pathologist is genuinely expert. These results, however, ought to be closely approached in every well organized clinic. Such scientific study of suspicious cases entails no hardship upon either the physician or the patient. It enables us to sift out, with reasonable precision, the cancerous from the noncancerous lesions, and saves many patients from unjustifiably radical procedures on the one hand, or deplorably insufficient procedures on the other.

A third recent study of this type, by Hirsch-Hoffman,[8] may be alluded to, bearing out as it does the trustworthiness of histologic diagnosis in competent hands. This author, in 1927, studied the case in which in the years 1923 to 1925, a histologic diagnosis had been made of benign cervical erosion. Of a total group of 241, it was possible to reexamine 195. No lesion was found in 152 of these, while in 25

cervical erosion was present. In all these, however, microscopic examination showed the lesion to be benign.

The very recent study of Pemberton and Smith[9] furnishes evidence along the same line. A follow-up of patients who had had cervical operations at the Free Hospital for Women, in Boston, showed that "not one patient whose cervical specimen was suspicious but not malignant has been found to have developed cancer, although sufficient time has elapsed since operation."

Several more points justify emphasis. In the first place, only a comparatively small proportion of cervical lesions call for biopsy. In the overwhelming majority, the diagnosis is reasonably plain from a clinical standpoint, and in these biopsy need not be done, or, if it is resorted to, the evidence afforded by it will usually be only confirmatory. Cancer of the cervix will rarely be found in cases which clinically present no suspicious features whatsoever. But it will not infrequently be found in cases which clinically are only suspicious. Since the vast majority of cases are either obviously benign or obviously malignant, biopsy will be indicated in only a small proportion of cervical lesions, probably less than 5 per cent. In cervical lesions, one has the great advantage of actually seeing and feeling the lesion. This, however, is not true of lesions of the endometrium, so that the proportion of cases in which the diagnosis must be made by the microscope is actually much higher.

Again, and especially in the matter of curetting for diagnosis, there are many cases in which the diagnosis can be made with reasonable certainty by the naked eye appearance of the removed tissue. Hyperplasia of the endometrium, retained gestation products, and adenocarcinoma, to mention only three of the lesions often encountered, all present, in typical cases, more or less characteristic gross pictures, upon which it is not necessary to elaborate here.

Finally, it need scarcely be said that the pathologist, no matter how expert he may be, encounters his pitfalls, like his clinical coworker. There is a small proportion of cases in which our present-day knowledge of cancer diagnosis, as applied to the individual case, simply will not permit of definite decision. In such cases the honest pathologist need not be ashamed to express his limitations. When a diagnosis is thus perforce held in abeyance, it is usually advisable and possible to hold treatment in abeyance also, and to repeat the biopsy or curettage in two or three weeks. In certain cases, the circumstances of the case may make it seem wise to proceed with radical measures on mere suspicion, but this policy should certainly not be made a general rule.

The introduction into clinicopathologic nomenclature of the term "precancerous" has done some good, but, perhaps almost as much harm. The harm has come chiefly from the fact that the frequent resort to radical treatment of lesions which are merely "suspicious"

has been justified in the minds of the offending surgeons on the ground that such lesions are "precancerous." There is no evidence as yet of an intermediate stage between noncancerous and cancerous disease, although there is much evidence to indicate that certain benign lesions, such as chronic inflammation, predispose to the development of cancer. If the term "precancerous" were always used in this sense, there would be little objection to it. But lesions "precancerous" in this sense do not call for radical measures for their removal. Corrective

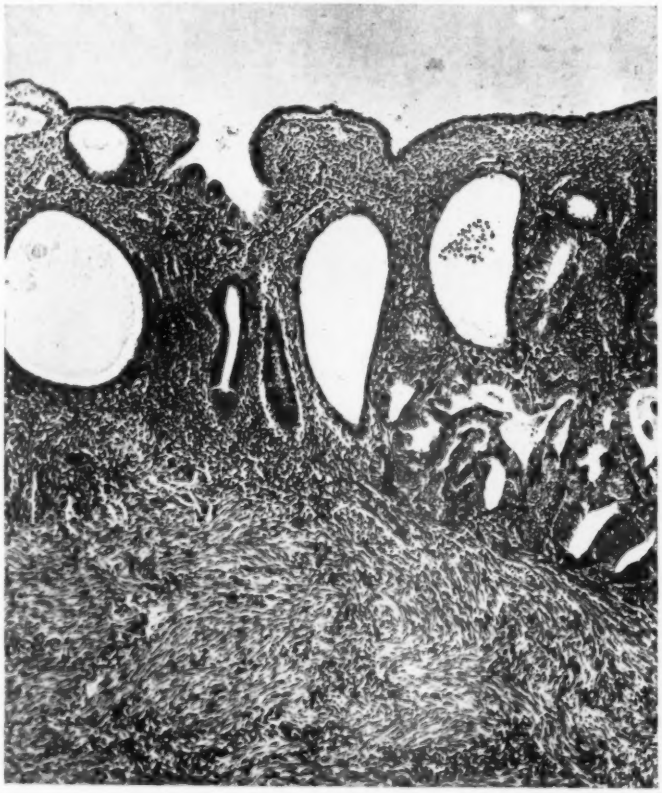

Fig. 11.—The growing margin of an adenocarcinoma of the body, showing the sharp line between the perfectly benign endometrial glands to the left (some distended by senile obliteration of the ducts) and the definitely cancerous glands to the right. Still further to the right, beyond the limits of the picture, is a large tree-like cancer growth, which shows little or no tendency to push into the underlying musculature.

measures of the most conservative sort will usually suffice, such as radial cauterization of a chronic erosion of the cervix. It is when the lesion is so marked as to become really "suspicious" that biopsy has its great field.

It is easy to believe that epithelial lesions of this type, in which there is a more or less marked hyperplastic tendency already, would step across the line into actual malignancy more readily than do the epithelial cells of the normal cervix. Nor does it seem unnatural to

think that they might at times be caught in a transition stage, if such a transition really occurs. But as yet the evidence is strongly against such a view. For example, the growing margins of a cancer are usually sharply marked off from the normal tissue, from a histologic point of view at least. This is well shown in adenocarcinoma of the uterus, where the margin often shows the characteristic cancer glands immediately adjacent to perfectly normal glands (Fig. 11). The latter, instead of being lighted up by the approaching cancer flame, are destroyed by the cancer, which derives its destructive growth from some innate character of its own cells.

There can be little doubt that, in addition to such local lesions in the cervix, there must be present a constitutional predisposition of some unknown sort before cancer can develop. But to minimize the importance of the local factor because of this fact, as some would do, is highly illogical. Both the constitutional and the local factors are important. The first we can do nothing to control, because we know nothing of its nature. On the other hand, the predisposing rôle of chronic irritating lesions has been established beyond reasonable doubt, and the eradication of such lesions is usually easily possible. In fact, it is about all we can do along the lines of actual cancer prophylaxis. The physician who is on the alert for cancer in its early curable stage will find many lesions which are not cancerous but which are of this distinctly predisposing type. The correction of such lesions will confer at least a measure of safety upon the patients thus treated.

The time will undoubtedly come when the diagnosis can be made earlier and more precisely than at present. Efforts are already being made along this line, especially by the method of differential staining. For example, Schiller[11] has recently been advocating the use of Lugol's solution of iodine to the gross lesion for this purpose, on the ground that the cancer cell contains no glycogen, while the normal cell does. Already, however, the evidence against the reliability of this particular test is quite convincing, but the possibilities along this general line are definite. The use of Hinselmann's colposcope, by means of which lesions of the cervix or vagina are studied by illumination and magnification, may be of auxiliary importance in certain cases. That it can achieve a more important position seems to be doubtful from the reports available in the German literature, where it has been much discussed. For the present, therefore, the microscope must remain the court of final resort in the diagnosis of cancer. Even now, as I have indicated, the proportion of error is not disturbingly high, and even this proportion should be lessened by the knowledge derived from a more widespread study of the disease in its earlier stages.

SUMMARY

This paper deals with the matter of pathologic differentiation in lesions of the uterine cervix or body, which clinically are suspicious of

cancer, i.e., those cases in which biopsy or diagnostic curettage is usually called for. While cancer will rarely be found where there is no clinical suspicion whatever of its presence, it is revealed in a not inconsiderable proportion of cases which clinically are only suspicious. In an even larger proportion such lesions will be found to be benign, so that a patient will be spared the misfortune of the unnecessarily radical treatment which would be entailed by a policy of operating "on suspicion," or because of a belief that the suspicious lesion is precancerous. Most lesions which are precancerous, in the sense of predisposing to cancer, in themselves are easily curable by simple conservative measures.

In the cervix, especially, pseudomalignant pictures are extremely common, especially with chronic inflammations and polypi, but, with few exceptions, the microscope will clear up the diagnosis and point the way to the proper treatment. These pseudomalignant lesions are discussed in the paper, more especially as they bear upon the diagnosis of cancer. As cases come to the gynecologist earlier, there will be an increasing proportion in which the microscope will be essential for making rather than merely confirming the diagnosis of cancer. In doubtful cases involving the endometrium, representing chiefly cases of uterine bleeding in women beyond thirty-five where an obvious cause is not present, the microscope is essential in a much larger proportion of instances. Follow-up studies have shown the general trustworthiness of microscopic examinations after biopsy and diagnostic curettage, for the microscopic diagnosis, when made by a competent pathologist, is rarely belied by the operative findings or the subsequent course of the patient.

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LEUCOPLAKIC VULVITIS AND CANCER OF THE VULVA (ETIOLOGY, HISTOPATHOLOGY, TREATMENT, FIVE-YEAR RESULTS)

By Fred J. Taussig, M.D., St. Louis, Mo.

IT IS not often in the study of cancer that, with increasing years, we become more and more optimistic. Yet such has been my experience with cancer of the vulva, for while in 1912 in my first report of 8 cases, I gave a gloomy picture of this disease, an analysis of the present series justifies the conclusion that next to cancer of the uterine body it is the most benign type found in the female genitals, since approximately 50 per cent can be prevented, and, of those cancers that have already developed, about 60 per cent can be permanently cured. If we do not attain such results, I am convinced this is due largely to a failure to appreciate the predisposing factors in the disease and the proper treatment for its cure. Because of the relative infrequency of the disease, many surgeons and gynecologists have not taken pains to study the operative technic and cases have only too often been given slipshod treatment with disastrous final results.

This paper is based on the study of 40 cases of leucoplakic vulvitis and 76 cases of cancer of the vulva observed since 1907. They do not include the cases of primary cancer of the female urethra, although those instances where the cancer took its origin from the vestibular skin surrounding the meatus were classified as vulvar tumors. If the total number of these cases (116) seems large, this has been due in part to the generous cooperation of my colleagues, Drs. Gellhorn, Crossen, Ehrenfest and O. H. Schwarz, some of whose cases (26 in all) have been included in my studies; in part also to my special interest in this subject for the past twenty years, because of which a greater number of these patients have been referred to me. A majority of them were observed and operated upon at the Barnard Free Skin and Cancer Hospital.

This whole subject has been given but scanty consideration in recent literature and in the last ten years practically the only important contributions were those by Giesecke, 44 cases (1921); Sabre-Casas and Carranza, 37 cases (1928); and Graves and Smith 15 cases (1929). In former communications I have taken up the literature previous to 1920. Those interested will find in Graves a full review of the literature pertaining to leucoplakic vulvitis and kraurosis. Hence, I refrain from going into that phase and will proceed directly with a narration of my own experiences, referring from time to time to the work of others in discussing certain points.

In addition to the 40 cases of leucoplakic vulvitis, there were 39 vulval cancers in which a leucoplakic vulvitis was coexistent. In almost all of this latter group at the time of operation, the entire vulva was removed as well as the cancer, so that the leucoplakic lesions were available for microscopic study.

I regret that Graves has seen fit to retain the term kraurosis in preference to leucoplakic vulvitis. He agrees that the latter name is more accurate but says general usage makes him prefer the term kraurosis. This seems illogical. We might as well continue indefinitely to refer to all toxemias of pregnancy as eclampsia instead of limiting it to those that terminate in convulsions. In similar wise I

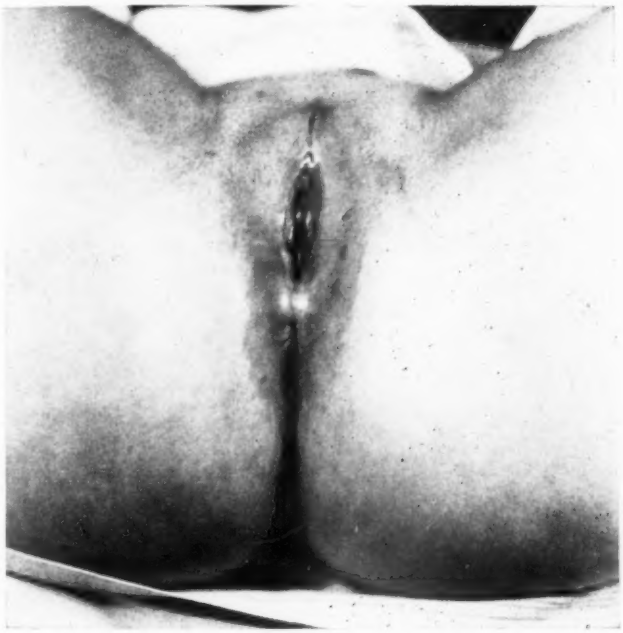


Fig. 1.—Leucoplakic vulvitis with kraurosis (early stage). The prepuce and perineum show leucoplakia while the labial region has the dusky red color known as "kraurosis rouge."

think we should limit kraurosis to those cases of leucoplakic vulvitis that terminate in obliteration of the labial and preputial folds.

LEUCOPLAKIC VULVITIS

The considerable majority of patients suffering from leucoplakic vulvitis have a symmetrical involvement of the entire nonhairy portion of the vulvar skin extending from the mons veneris to the margins of the anal ring. Occasionally the lesions are found to extend for a distance of 2 to 3 cm. around the anal ring. Of this generalized symmetrical type I found 28 out of 40 in my series. The lesions were not always found equally pronounced over this entire area. In fact it was the

rule that the leucoplakia was more definite in the preputial folds above and in the perineoanal region below, the itching sensation being more marked about the clitoris and the anal folds. In 6 of my series there was symmetrical localization of the disease over the perineum and around the anus without any lesions about the labial and preputial folds. In the remaining 6 cases the leucoplakia was over a smaller patch located asymmetrically and at times limited to only one side of the vulva.

The obliteration or flattening of the labial and preputial folds to produce the condition known as kraurosis was present in 22 of the cases but not in every instance was this kraurosis equally pronounced. At times a small ridge was present in the upper labia minora and prepuce, at times they were practically flush with the surrounding skin, leaving only a dimple in the region of the minute gland of the clitoris. To some degree the extent of the kraurosis was in direct proportion to

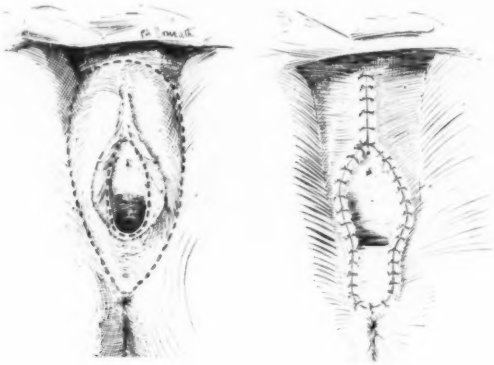


Fig. 2. Fig. 3.

Figs. 2 and 3.—Vaginal flap operation for leucoplakic vulvitis. After removing the involved vulvar skin, the posterior vaginal wall is dissected free, and, after a cut into each lateral vaginal sulcus, the flap is drawn over the perineum and anchored to the anterior margin of the anus with interrupted stitches. (From Nelson's Looseleaf Surgery on Gynecology, pp. 678, 679.)

the severity and duration of the inflammatory process. Unfortunately only a small number of patients were observed within the first year or two of the disease. The majority had had symptoms for a long time before they finally made up their minds to seek medical advice. In these earlier cases the gross appearance was different. The leucoplakic areas were in spots or ridges over the prepuce or perineum or between the anal folds, while the remaining skin, though dry and flabby in tone had either a greyish-pink or dusky red color. In several of the early cases this dusky red mottling in the region of the labia minora to either side of the introitus vaginae was quite characteristic. Jayle, who made similar observations, called this lesion "kraurosis rouge." Even in this early stage, however, one notices the marked brittleness of the skin. Simple separation of the labia for inspection will often produce a superficial crack in the epidermis especially over the peri-

neum. In the more extensive and older lesions the entire skin assumes a thin parchment-like appearance with patches of greater thickness and whiteness and numerous superficial excoriations produced by the scratching.

From a racial standpoint it is of interest that the material for this report came largely from clinics where about 50 per cent of the clientele were colored women, yet only one case in this series of 40 was found in a negress. This patient had a large leucoderma over the upper vulva and it was at the edge of this leucoderma that there developed over the labium minus a small area of typical leucoplakic vulvitis. At this time it should be mentioned that in one case of carci-

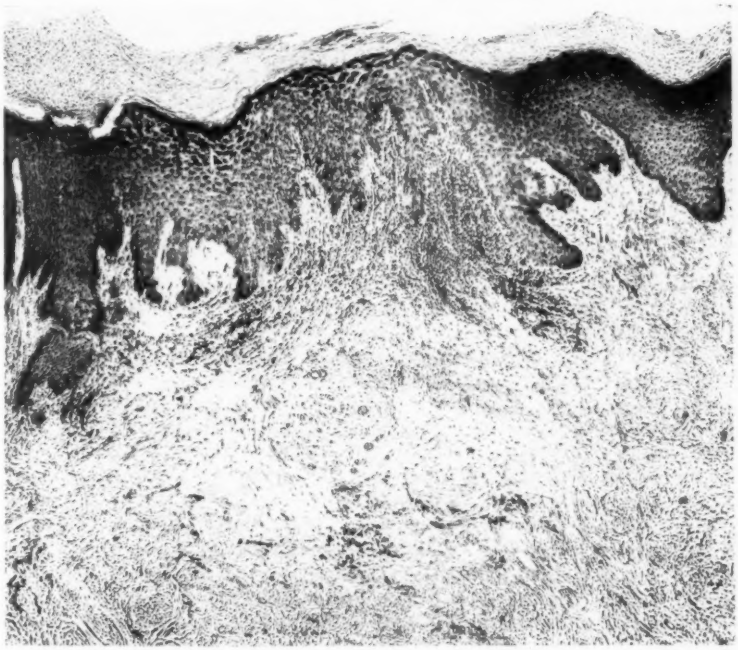
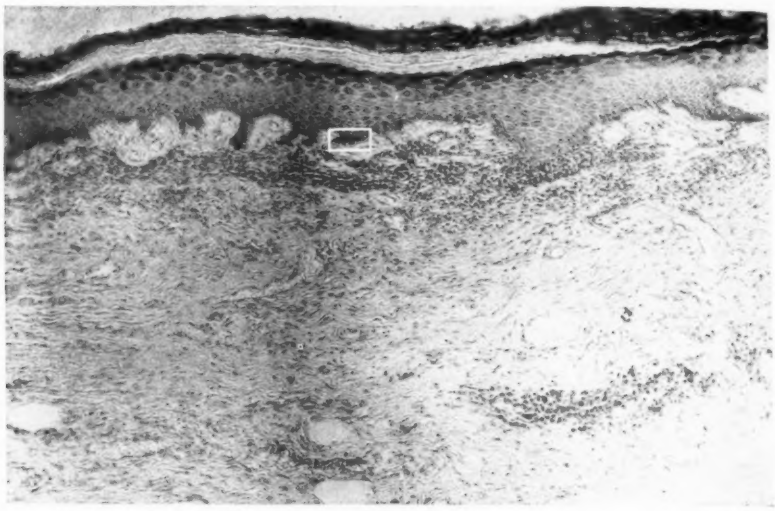


Fig. 4.—Leucoplakic vulvitis: hyperplastic stage. Note from above downward, first, the greatly thickened layer of keratin cells (hyperkeratosis); second, the increased number of eleidin cells, forming an almost black band; third, the granular zone sending long papillary processes of epithelium into the connective tissue (acanthosis); fourth, the connective tissue showing marked round cell infiltration, most marked directly beneath the epithelium.

noma of the vulva in a negress the disease developed upon a definite preputiolabial leucoplakia (see Fig. 9). From this it seems reasonable to assume that the greater elasticity of the negro skin, as witnessed by the rarity of perineal tears at childbirth, is a factor predisposing against the development of leucoplakic vulvitis in this race.

That leucoplakic vulvitis usually follows a cessation of ovarian function has been sufficiently emphasized in previous articles. In 30 out of the 40 patients in my present report this was the case. The average age of the patients was forty-nine years, the oldest one being seventy-



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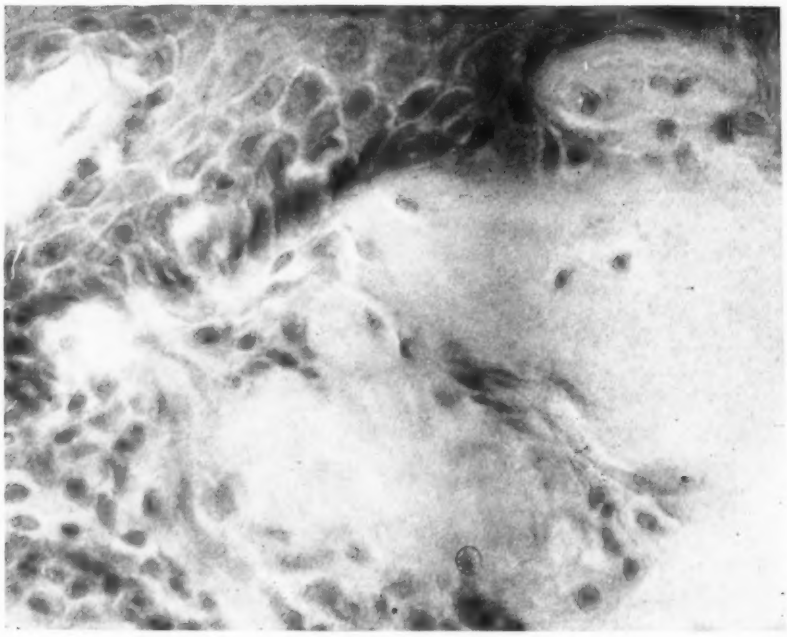


B.

Fig. 5.—Leucoplakic vulvitis. A stage midway between the hyperplastic and atrophic condition: (*A*) low power field, showing a zone of pigmented hyperkeratosis, eleidin layer still marked, epithelial layer sending short processes downward, and beginning development of collagenous areas in the connective tissue directly beneath the epithelium; (*B*) high power of area outlined in (*A*) showing collagen formation in the connective tissue.

four and the youngest twenty-six. Of the 10 patients who had not yet reached the menopause, some abnormality of menstrual function was noted in all, although this was not always pronounced. One of the

most interesting in this regard I had occasion to observe only a few months ago. She was a young married woman of twenty-six years, who stated that ever since the onset of menstruation at the age of fourteen, she had suffered from a pruritus of the vulva, that became increasingly severe with each year. Although married for over a year sexual intercourse had been impossible owing to a kraurosis of the vaginal introitus resulting from this leucoplakic vulvitis. Microscopic examination of the vulval tissues after vulvectomy in this case showed the typical lesions found in this disease.

Sterility is not in any special way associated with the disease. Where such a vulvitis occurred after the menopause, it was found as often in women who had had many children as in those who had had none. In one woman pregnancy occurred for the first time after removal of the leucoplakic vulva. In another the lesions were seen for the first time coincident with a pregnancy.

Pruritus of long standing is the almost unfailing symptom of leucoplakic vulvitis. There were but one or two exceptions to this rule and in them the lesions were still very slight and the patients stated that the vulval skin in this region felt dry and sore. The duration of the pruritus before treatment was carefully noted in 27 patients and averaged over five years. In seven instances it had lasted from ten to fifteen years before the patient came under our observation. So intense was the pruritus that many of the patients were "nervous wrecks," suffering from insomnia, for it was the invariable rule that the pruritus was more severe at nighttime.

Burning after urination was present if there was marked excoriation of the vulva. Pain on defecation was noted if the anal lesions were pronounced. A not inconsiderable number had a pronounced vaginal discharge, which added to the chafing of the vulval skin. In many of the patients with kraurosis, dyspareunia was so marked that sexual intercourse was no longer attempted.

The clinical course of the disease is usually a slowly progressing one, although in some instances there are long periods where the process remains stationary or diminishes in severity. It is difficult in view of the rarity of both leucoplakic vulvitis and cancer of the vulva to follow any appreciable number from the stage of leucoplakia to that of malignant change or to determine accurately the percentage of this form of vulvitis that eventually becomes malignant. If however over a certain period of time I have had occasion to see 40 cases of leucoplakic vulvitis without carcinoma and 39 cases of leucoplakic vulvitis with carcinoma, I think it can be assumed that in the course of the disease, eventually at least one-half will undergo a malignant change. As to a stage of complete healing of leucoplakic vulvitis described by Berkeley and Bonney I have seen many temporary alleviations but

I know of no five-year cures, spontaneous, medical or radiotherapeutic. For a short time the vulvar skin may look fairly normal but apparently the underlying pathology sooner or later starts off the process anew, and final relief is secured only by a complete vulvectomy.

Treatment.—An analysis of the treatment given these 40 patients shows that 25 were subjected to a more or less complete vulv ctomy depending on the location and extent of the vulvitis. Some of the remainder refused further treatment when operation was suggested, or were given antipruritic salves and lotions. In 3 patients radium was used and in 3, x-ray therapy, but none of these six patients were more

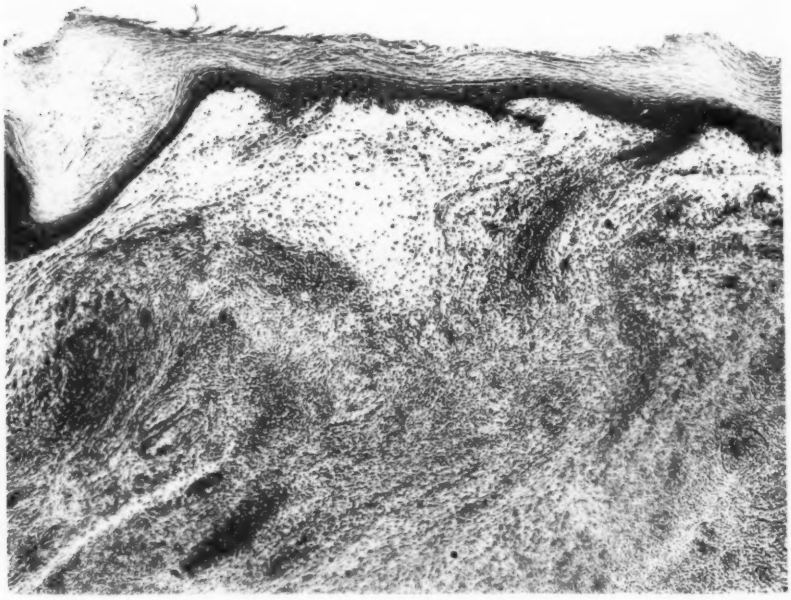


Fig. 6.—Leucoplakic vulvitis: atrophic stage. Here we see an area of pronounced hyperkeratosis, beneath which is a greatly thinned strip of epithelium, 3 to 4 layers, with few eleidin cells, an irregular, frayed out basement membrane, and only here and there a few short projections of epithelium into the subjacent connective tissue. The connective tissue shows large areas of collagenous deposit with zones of pronounced round cell infiltration. In some instances the sclerosis is more marked with less evidence of inflammatory changes.

than temporarily relieved by this procedure. The radium cases, although only gamma irradiation was employed, showed a prolonged radium reaction with superficial radium ulcer (average dosage 500 mg. hr.). The results of irradiation in any form were certainly very discouraging, although other observers seem occasionally to have met with success. Four of the 6 patients in my series were subsequently subjected to a vulvectomy. The use of corpus luteum and ovarian extracts was equally unsatisfactory. Occasionally a patient would seem to be temporarily relieved. One patient reported after a five-year period that

by the regular use of vaginal antiseptic douches the pruritus was completely relieved and while the skin still showed definite leucoplakic changes, she was symptomatically well.

A special effort was made to follow up the patients over a period of years. Of the 23 vulvectomies, 4 were lost track of; 2 died, one died on the fourteenth postoperative day of coronary embolus, and the other died within a year following operation of tabes dorsalis. Of the remaining 17 patients, 16 were cured, 9 of them for periods longer than five years. These patients were all personally reexamined by me. Two

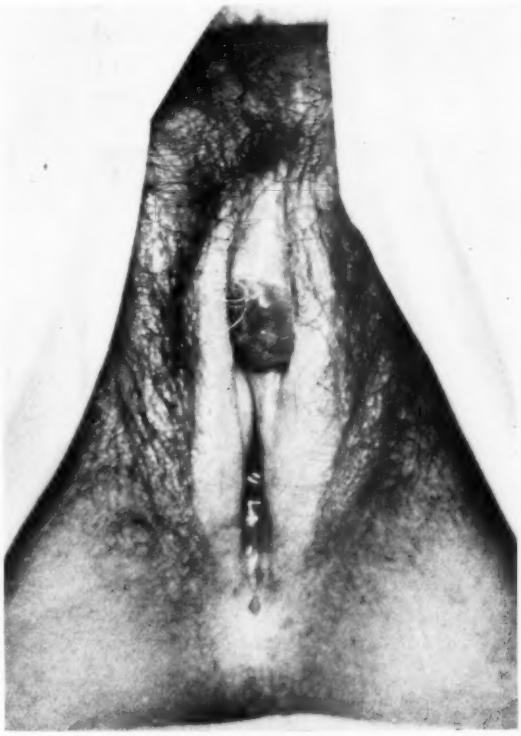


Fig. 7.—Carcinoma of the prepuce of the clitoris, an everting cauliflower nodule developing from the parchment-like leucoplakic vulvitis involving both labia, prepuce and perineum.

patients showed a small patch of keratosis near the anal margin, appearing in one, six years, in the other, eleven years after vulvectomy. These patches were less than 5 mm. in diameter and were easily and permanently removed by electrocauterization. One patient with a more extensive recurrence over the perineum two years after vulvectomy will require a second operation. The final result of vulvectomy may therefore be described as entirely satisfactory.

The relief from the tantalizing pruritus by means of vulvectomy is most striking. Even in the first few days the pain of the sutures and wound seems light compared to the suffering and insomnia produced

by the pruritus. In my earlier operative experience I had much difficulty in obtaining good wound healing. Particularly over the perineum, sutures would cut through and a large area heal by granulation with a stiff rigid scar. Another complication was the painful stenosis of the anus that often followed a complete removal of the perianal skin. To overcome these difficulties I have devised a modification of the usual technic of vulvectomy as follows:

Vaginal Flap Operation.—After removing the entire nonhairy portion of the vulva from the mons veneris to the anterior anal margin, including the prepuce, clitoris, labia minora, inner aspect of labia majora, and perineal skin, all bleeding points are caught and ligated. Then the posterior vaginal wall is dissected free from the rectum and levator muscles, as in a perineorrhaphy, for a distance of about 6 to 7 cm.

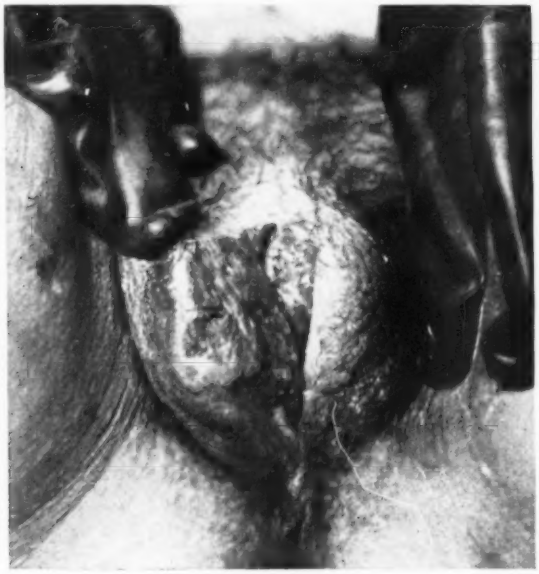


Fig. 8.—Early inverting carcinoma of the right labium, springing from an asymmetrical leucoplakia of the upper vulva. Epidermal type.

upward. A cut 3 cm. along each vaginal sulcus will now mobilize this flap and permit it to be drawn outward over the perineum so that it can be sutured to the anterior margin of the anal ring (Fig. 2). In this way it fills in the gap between vagina and anus, which it is usually difficult to cover by the neighboring skin without tension and without producing a painful cicatrix at the entrance of the vagina. I have now done this type of plastic closure of a vulvectomy in 6 cases of leucoplakic vulvitis with uniformly satisfactory results. In only one instance was there a partial slough along one edge of the vaginal flap.

Double Anal-Bridge Operation.—To overcome the tendency for the anal mucosa to break loose and retract where it is tacked directly to the

outside skin after extensive circular removal of the perianal leucoplakic skin, I have in my last case of this kind left intact a bridge of anal skin on either side, about 1½ cm. in width. Even though a small patch of leucoplakia may be present on such an anal bridge, the cutting off of the tributary nerve supply prevents a return of the pruritus. By thus keeping a grasp on the anal mucosa on either side, we can proceed above and below with fairly extensive removal of the affected skin without danger of producing a stenosis and extensive and painful scar-tissue formation around the anus. This complication of painful anal strictures has been one of the most annoying complications of the complete vulvectomy in the past, and the results obtained in this first case justify the feeling that the use of the double anal bridge will greatly improve the postoperative course in these cases.

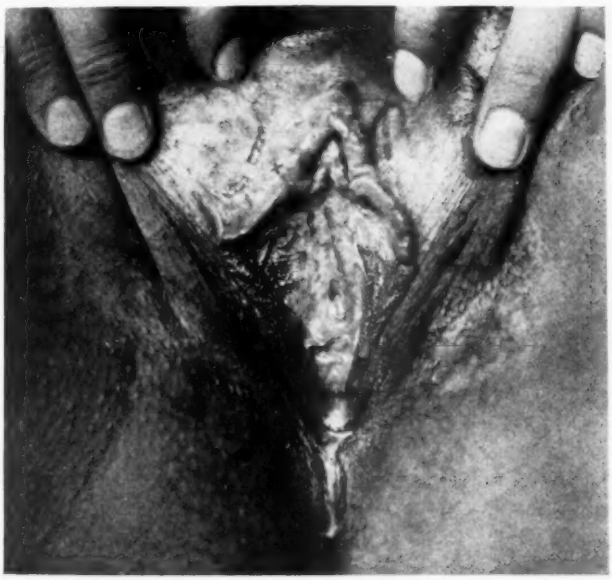


Fig. 9.—Leucoplakic vulvitis in a negress involving labia minora, prepuce and adjacent skin with a beginning carcinoma of the right prepuce at point marked x.

Histopathology.—Material for histologic study was obtained in 25 of the cases of uncomplicated leucoplakic vulvitis, and in 39 of the cases in which it was found in combination with carcinoma of the vulva. In almost every instance sections were made from 4 or 5 different blocks, so that the present conclusions are based on a study of over 500 sections made in 64 cases. Naturally there was considerable variation in the nature and extent of the lesions found and even in the same case there was often a decided difference between sections taken from various portions of the affected skin. In general, however, I have found little to change the observations as stated in previous publications. The most important variation is in the direction of greater simplicity, for instead of dividing the condition into three or four stages as was

done before, I think it more logical to divide this condition simply into an early hyperplastic stage and a late atrophic stage.

In the early stage we find extensive subepithelial leucocytic infiltration with pronounced elongation of the epithelial papillae (acanthosis) and beginning thickening of the keratin layer. In the beginning, nuclear elements are still present to some degree in this keratin layer and the term parakeratosis has been applied to this stage in distinction from the later hyperkeratosis where only thickly packed keratin fibers are found. In the course of a few months or a year if the pruritus has been pronounced there is noted a marked increase in the thickness of the eleidin layer and in the quantity of eleidin deposited in these cells. Since this substance stains very deeply with hematoxylin this layer often appears as a thick black band beneath the keratin. The epithelial layer in this early hyperplastic stage is as a rule from 4 to 6 times thicker than in the normal individual. In the connective tissue there is considerable hyperemia and marked round cell infiltration. Only toward the conclusion of this stage do we notice increasing connective tissue formation with some sclerosis.

Fig. 10.—Multiple carcinoma of the vulva on a basis of leucoplakic vulvitis. Where an incomplete vulvectomy is done in cancer on a leucoplakic basis, a new cancer may spring from the remaining area of leucoplakia. Three instances of this sort occurred in my series. The lymph glands in the case photographed above showed carcinoma (Fig. 17). Patient is free of recurrence five and a half years since operation.

The late atrophic stage is not an abrupt change. There are gradations between it and the hyperplastic stage so that areas midway between the two are commonly found. Yet the lesions of this late stage are so characteristic and different from the early stage that it seems histologically almost like two diseases. As we approach the late stage we observe increasing hyperkeratosis, pronounced eleidin but lessened

acanthosis. The papillae become much flatter and shorter, even though the total thickness of the epithelial layer is still twice that of the normal. There is also diminished round cell infiltration and increasing selerosis of the dermis.

The typical late atrophic stage is a very distinctive picture. It is the one described by Breisky and found almost invariably in those cases with obliterated labial and preputial folds (kraurosis). Since it is however also found just as pronouncedly in lesions located in the perineal and anal regions, without any general vulval flattening, we

Fig. 11.—Carcinoma of the vulva springing from the left upper edge of a syphilitic tertiary ulcer. Vestibular type.

cannot call this stage, as Graves does, kraurosis. The epithelial layer in these cases consists of a considerable layer of hyperkeratosis, beneath which is found a thin layer of eleidin cells, and then, with papillae absent, a flat strip of pavement cells that may or may not be covered by a single layer of basement epithelium. In many areas the border of this pavement epithelium appears frayed out and irregular without any sharp distinction from the connective tissue beneath. Even more marked are the changes in the dermis. The round cell infiltration is in more or less circumscribed lymph zones, much less marked than in

the early cases, with plentiful plasma and mast cells scattered through the connective tissue. This connective tissue in many areas directly beneath the epithelial layer undergoes a peculiar collagenous change, forming patches of glairy tissue containing only a few normal cells.

I have left to the last a description of the elastic tissue in this disease since it has rightly been emphasized in all descriptions as of great significance. Even in the earliest lesions examined* I never failed to note some diminution in the amount of elastic tissue between the epithelial papillae of the skin and directly beneath the basement membrane; this absence of elastic fibers became increasingly marked as

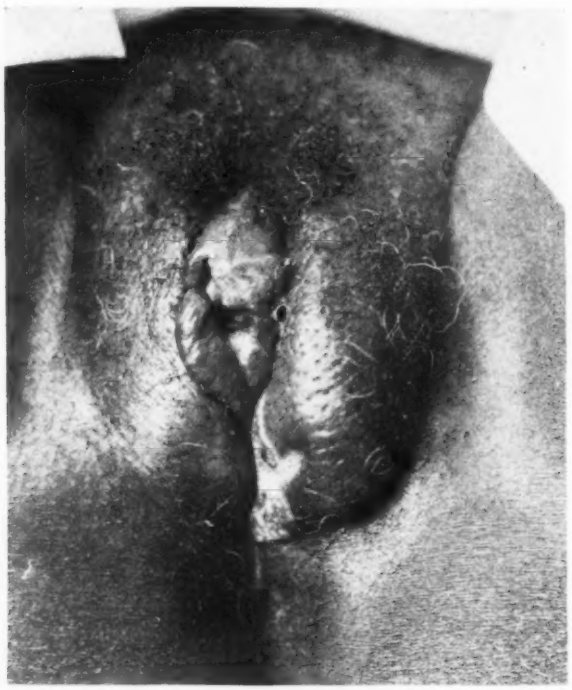


Fig. 12.—Carcinoma of the vulva developing on a tertiary gumma with hypertrophic vulvitis in a negress.

the disease advanced and was most pronounced in the late atrophic stage of the disease. There was complete absence of these fibers in the upper dermal zone, but directly beneath this area where you first noted the elastic tissue, it was piled up like kindling wood in irregular pieces and strips, so that you had the impression not of absent, but rather of dislodged, disintegrated, elastic fibers.

A study of the 39 cases in which carcinoma was implanted on a leucoplakic base revealed histologically that in 60 per cent the malignant changes took place in an early hyperplastic area and in 40 per

*In three private patients under previous treatment for other conditions, the leucoplakic vulvitis was noted within a few months of its onset.

cent in a late atrophic area. Hence carcinoma may develop at either stage of the disease, although it is a little more prone to spring from the hyperplastic lesions.

Conclusions.—From the clinical and pathologic evidence of leucoplakic vulvitis thus far obtained, I think it reasonable to assume that in certain individuals as a result of an alteration or cessation of ovarian hormones there occur changes in the elasticity of the skin which lead to increased friability of the epithelial covering. In the presence of a vaginal discharge or even without it, minute multiple subepithelial infections occur, which by swelling of the neighboring

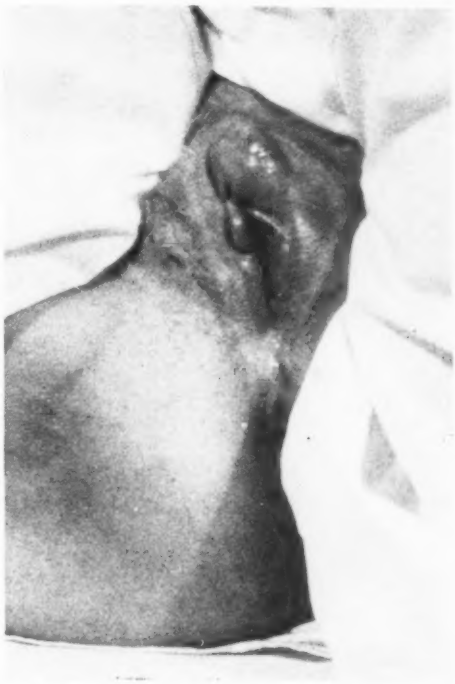


Fig. 13.—Carcinoma of the glans clitoridis. Note the absence of leucoplakia and the subdermal development of the tumor.

tissues produce a feeling of itching. This pruritus in turn leads by scratching to increased traumatism of the affected skin and so a vicious circle is started that results first in a chronic infection, then in epithelial hyperplasias and finally in certain sclerotic atrophic changes.

CARCINOMA OF THE VULVA

Only about one out of every 20 or 25 cancers in the female genital tract arise from the vulva. If the proportion was relatively greater in my series, it was probably because my material came largely from a skin and cancer hospital, to which skin cancers of all sorts were widely referred. The average age of my patients was fifty-nine in vulval

cancer in contrast to forty-nine in leucoplakic vulvitis. The youngest patient in my series was twenty-six years of age and the oldest one eighty-seven years. Only 3 patients out of 76 were colored women, a relatively small proportion and in 2 out of these 3 the carcinoma developed not from a skin lesion but from the edge of an old syphilitic ulcer at the fourchet.

Anatomical Forms.—Carcinoma of the vulva is by no means a single disease, for upon closer study we find that there are four definite and distinct forms, varying decidedly in accordance with the point of origin of the tumor. This point has I believe not heretofore been stressed as it should have been. These four forms are:

1. Epidermal
2. Clitoris
3. Vestibular
4. Bartholin gland

1. The *epidermal* form is by far the most frequent. Out of the 67 cases of my series in which a fairly definite classification could be made, 51 sprang from the labial, perineal, or preputial skin. Only in the very early cases could a differentiation between labial and preputial origin be made, but the fact that in 9 instances the onset was clearly in the region of the prepuce speaks for the relative frequency of this type. In the past this preputial cancer has been wrongly classified as carcinoma of the clitoris. It resembles closely in etiology, spread and histologic structure the form found immediately adjacent in the labial skin. Let us not forget that the prepuce is anatomically merely an extension of the labial folds. Etiologically this epidermal cancer springs from leucoplakic vulvitis in almost every instance. Occasionally warts or traumatic scars may be a factor.

2. True carcinoma of the *clitoris* is a very rare and interesting disease. As seen in Figs. 13 and 14 the cancer begins beneath the surface of the skin in the epithelium of the glans itself. Histologically it presents a very different picture. The cells are smaller and more rounded and the nests are more loosely formed so that in areas there is a resemblance to sarcoma. Apparently this is a very malignant tumor for the cells are of undifferentiated embryonal type, and there are very numerous mitoses. Only two of the cases in my series were of this clitoris type and neither of them were associated with leucoplakia of the neighboring skin. The etiology of these tumors is unexplained.

3. *Vestibular* carcinoma was present in 10 cases in my series. The vestibular epithelium resembles more closely that found in the vagina than that of the epidermis. The type of carcinoma that springs from it also has distinguishing characteristics. It forms superficial indurated ulcers. Those situated near the urinary meatus are relatively

benign, but those that originate around the vaginal orifice tend to invade the vagina and then assume all the malignancy of a vaginal cancer. Eight of the 10 vestibular cancers in my series developed at the edge of an old syphilitic ulcer. From this it would appear that the etiologic association of syphilis in this type is just as definite as is that of leucoplakic vulvitis in the epidermal type. Histologically and clinically these cancers are malignant, they show nests of medullary undifferentiated epithelium with many mitoses.

4. *Bartholin gland* cancer has been long recognized as a special type. It may be either squamous or adenocarcinomatous but always begins as a subepidermal tumor as shown in Fig. 16. There were 4 Bartholin gland tumors in my series. In 3 of these a definite history of a pre-

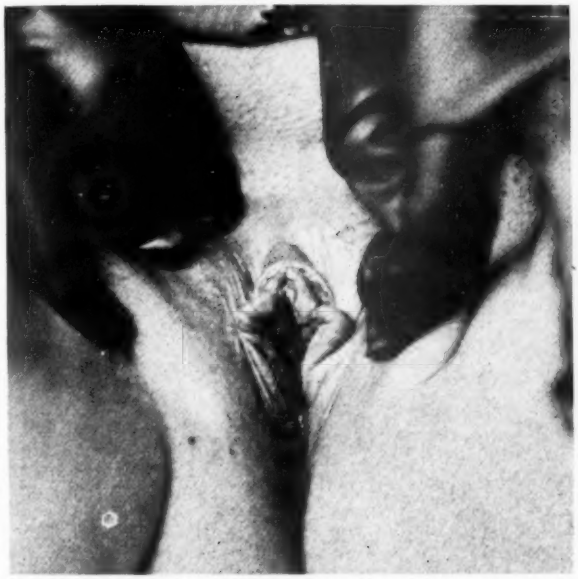


Fig. 14.—Carcinoma of the glans clitoridis with perforating ulcer but no involvement of the prepuce or labia.

vious Bartholin gland infection was obtained; once the gland had been incised. The tumor, because of its location beneath the epithelium, reaches a considerable size before it causes enough discomfort to compel the patient to seek medical advice. Hence, fewer of these cases are cured.

The lymphatic spread of all 4 types of vulval cancer is similar: at first to the superficial inguinal and femoral, then to the glands just beyond the inguinal canal and those internal to the femoral ring, finally to the iliac and aortic lymph glands.

The subject of the etiology of vulval carcinoma has been treated at length in my previous publications. Without giving at this point the clinical and histologic evidence on which this diagnosis of etiology is

based, I can say that an analysis of my cases shows the following distribution:

Leucoplakic vulvitis	39 cases
Syphilis (tertiary ulcers)	8 cases
Condyloma acuminata senilis	2 cases
Chronic bartholinitis	3 cases
Trauma	3 cases
Uncertain	21 cases

I was greatly interested in the study made by Smith in his joint publication with Graves. He found in an examination of 21 specimens of vulval carcinoma in his laboratory that 16 showed leucoplakic changes. This would make a ratio of 75 per cent of cancers due to

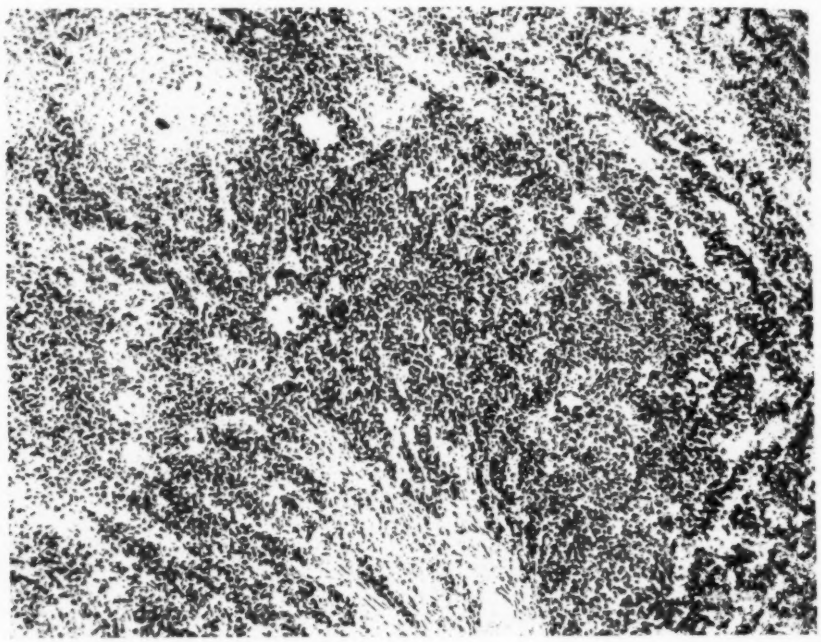


Fig. 15.—Carcinoma of the glans clitoridis. Microscopic section taken from case shown in Fig. 13. Note the sarcoma-like character of these tumors. They are very malignant (Malignancy index Type 4).

leucoplakic vulvitis. While in my series the percentage definitely due to leucoplakia is only a fraction over 50 per cent it should be remembered that Smith is dealing only with specimens from operable cases while I have included every vulval cancer that came under observation even though inoperable. If I had taken only the 49 cases in which a vulvectomy was done, it would have shown 39 cases of leucoplakia or about 80 per cent. These figures correspond closely to Smith's and indicate the greater operability of those cancers that develop on a leucoplakic basis.

The development of cancer of the vulva on a syphilitic basis has been carefully described by Dr. Gellhorn, including several cases in

this series. Fig. 11 is an excellent instance of a very early lesion developing on the upper edge of a typical tertiary ulcer. The interesting clinical fact of this group of 8 cases is the relatively high percentage of negresses, and the development of the carcinoma at an average age of thirty-eight in contrast to an average of sixty-four years for those cases where the cancer developed from a leucoplakic vulvitis.

The symptoms and course of carcinoma of the vulva need no special amplification. Pruritus was present in practically all cases preceded by leucoplakia. The ulcer produced a feeling of soreness with burning in the wound after urination. Bloody discharge was present but very

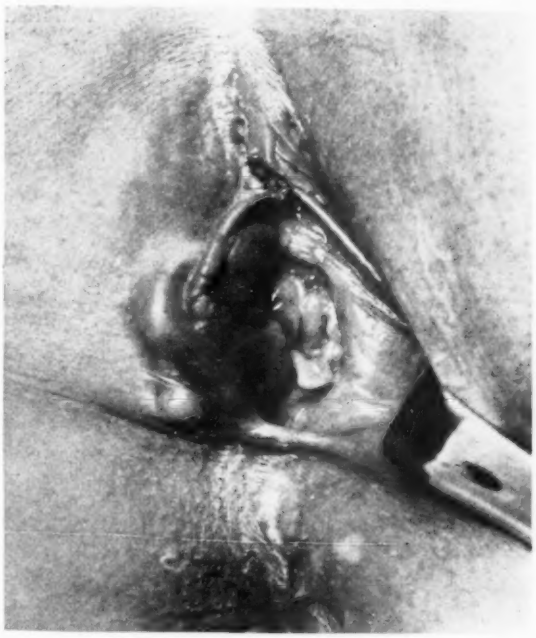


Fig. 16.—Carcinoma of Bartholin's gland. A history of previous Bartholin infection was here recorded. Note subdermal development.

rarely any extensive bleeding; pain in the more advanced cases radiating down the legs with an increasing edema of the legs as the disease advanced; relatively early metastases to the tributary inguinal and femoral glands and relatively late metastases to more distant glands and organs.

Although there is always some artificiality in any method of dividing cancers into groups according to the amount of involvement, I have attempted to do this for carcinoma of the vulva in the following way:

Group I. Cases without palpable metastasis, tumor 1 to 3 cm. in average diameter.

Group II. Cases without palpable metastasis, tumor 4 to 7 cm. in average diameter.

Group III. Cases with ulcer over 7 cm. in average diameter or deeper infiltration or palpable gland metastasis.

Group IV. Large ulcer with vaginal involvement or large cancerous lymph glands.

Group V. Far advanced tumors with broken down lymph glands and cachexia.

All cases in Groups I and II and most cases in Group III would be classified as operable; the remainder as inoperable. In my series there were found: Group I, 17 cases; Group II, 17 cases; Group III, 19 cases; Group IV, 16 cases; Group V, 7 cases. This would point to an operability of about 60 per cent. However 4 of the cases in Group I and II refused operation and in another patient the extreme age, eighty-seven years, made any such procedure seem inadvisable.

Malignancy Index.—The interesting and valuable observations regarding the malignancy index in cancer of the cervix made by Martzloff, Schmidt, Healy and others, led me to go over all my material with this in view to determine the value of a malignancy index in cancer of the vulva. Out of 76 cases in my series, the lesions were far advanced in 12 and no tissue was removed for diagnosis. In 6 cases tissue was removed for diagnosis but the sections were for some reason not available or suitable for the purposes of this examination. There remained then 58 cases that could be studied. In practically every instance a large portion of the tumor or the entire vulva was available for study and sections were made from various areas. I have tried to follow Broders' idea in dividing the cases into 4 types in accordance with the amount of anaplasia. Special attention was paid to cellular overgrowth, variation in size, shape, and staining qualities of the cells and their nuclei, infiltration tendencies, number and character of mitoses, connective tissue reaction. Dr. Jorstad, pathologist of the Barnard Free Skin and Cancer Hospital, checked my findings and was in agreement in practically every case.

Of Type 1, in which the cells were well differentiated with large areas of well formed pavement epithelium and large areas of pearls and but very few atypical cells or mitoses, there were found 7 cases.

Of Type 2, in which there was also well-developed pavement epithelium with occasional pearls but with a definite rim of atypical, deeply staining cells showing more numerous mitoses, there were 30 cases.

Of Type 3, in which the cells were grouped in medullary nests with only occasional small areas of a pavement-type cell, with plentiful mitoses, there were 16 cases.

Of Type 4, in which the structure of the tumor was loose, the cells spindle-shaped or markedly polymorphous, with giant cells, and countless mitoses, there were 5 cases.

The relationship of this malignancy index to the amount of involvement proved rather interesting and may in a sense be regarded as evidence of the value of such a histologic classification. The findings were as follows:

Group I (Ulcers 1 to 3 cm.) showed Type 1 = 5, Type 2 = 8 } average 1.61

Group II (Ulcer 4 to 7 cm.) showed Type 1 = 2, Type 2 = 9, Type 3 = 2, Type 4 = 2 } average 2.26

Group III (Infiltrating ulcers) showed Type 2 = 7, Type 3 = 8 } average 2.53

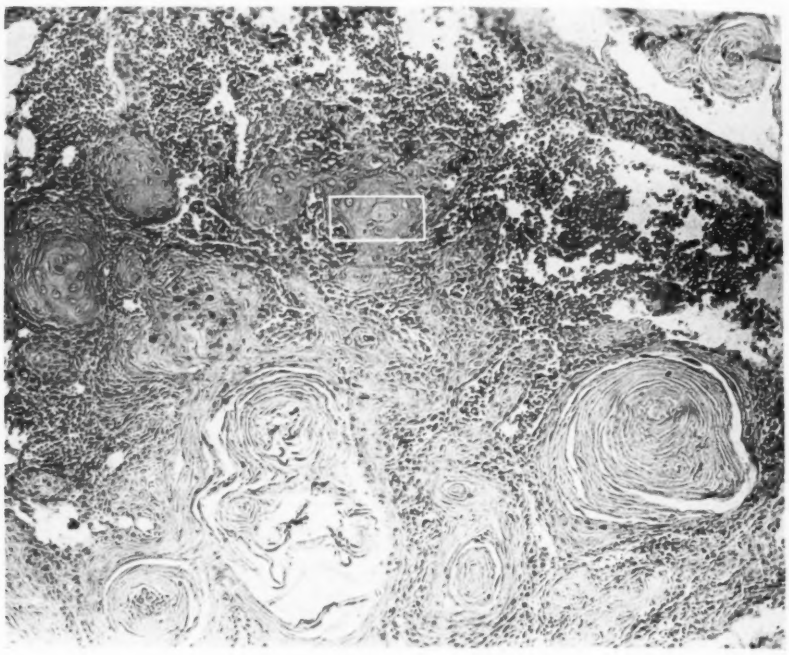
Group IV (Large ulcers with carcinoma in glands) showed Type 2 = 4, Type 3 = 4, Type 4 = 2 } average 2.80

Group V (Large tumors, necrosis, cachexia) showed Type 2 = 2, Type 3 = 2, Type 4 = 1 } average 2.80

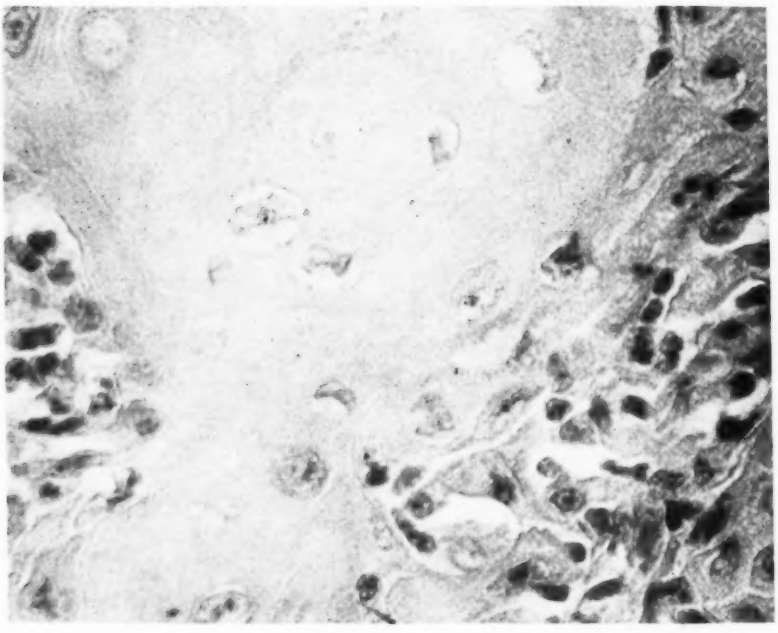
Thus we see that the cases that spread most rapidly and extensively showed the highest malignancy index. It is of special interest that the malignancy index in the epidermal cancers was much lower than was the case in the vestibular, clitoris or Bartholin gland tumors. Especially the cases that developed on a syphilitic basis in younger persons and those originating in the glans clitoridis showed a high malignancy index.

Treatment.—It is not surprising in view of the extreme age of some of these cancer patients that all treatment is at times refused. Six of our 76 patients were either untreated or else referred back to their family physicians for palliative measures. Of the remainder 21 were given some form of radiotherapy (radium or x-ray or both), and the other 49 were subjected to some form of surgical operation, either a partial or complete vulvectomy (15 cases), a vulvectomy combined with superficial or incomplete gland removal (18 cases) or a vulvectomy with double-sided complete Basset removal of glands (16 cases).

Radiotherapy.—With increasing experience I have become more and more discouraged at the results of radiotherapy in these cases. I believe that any dosage sufficient to cause even a temporary retrogression of the tumor is very apt to produce a radium burn. Such burns about the vulva may appear many months after the irradiation. They are always excruciatingly painful and slow to heal. I have been repeatedly amazed at the hypersensitiveness of the vulval skin to such rays. The practically uniform failure of either x-ray or radium to produce even a temporary alleviation of symptoms or appreciable diminution in the size of the tumor leads me to the conclusion that radiotherapy is not only of no avail but that it is as a rule actually contraindicated. It seems to stir things up and lead to more rapid metastases. The only exception I would make is in the use of radon gold seeds implanted into the primary tumor, where surgery for some reason is refused or contraindicated. Bailey's immediate results were rather encouraging. I had one similar local retrogression for one and one-half years after



A.



B.

Fig. 17.—(*A*) Lymph-gland metastasis from case of vulval carcinoma depicted in Fig. 10. Malignancy index in this case was Type 1. (B) High power microphotograph of area outlined in Fig. 17-*A*, showing high degree of differentiation into pavement epithelium.

radon gold seeds, but of course the tributary glands in this case became enlarged and then had to be removed surgically. In 3 cases where radium was implanted as needles or seeds into cancerous lymph glands no benefit was noted. Sobre-casas, Giesecke, and others have had equally discouraging results with radiotherapy. Only from the Radium-hemmet of Stockholm come more encouraging reports, but here the radiotherapeutic measures were used in combination with the destruction of the tumor by electrocoagulation (diathermy). I have the impression that it is the diathermy that is largely responsible for whatever benefit the treatment may have produced. Even so, only 8 out of the 26 cases treated between 1922 and 1924 were symptomatically well and only one case for as long as three years. The fact that in this report the statement is made that operations for carcinoma of the vulva are almost always hopeless indicates sufficiently the rather warped point of view on this subject by the writers.

Surgery.—In the period between 1906 to 1915 relatively few cases were seen, and these were operated upon either by simple vulvectomy or by a removal of the superficial femoral and inguinal glands in combination with the vulvectomy. If in the cases since 1915 there was no fixed rule regarding the operative technic, this was due in part to the fact that the other surgeons in charge of the cases were not convinced of the necessity of such a radical double-sided gland dissection and in part to contraindications in the physical condition of the patient to extensive operative measures. In 3 patients adhesions between a cancerous lymph gland and the sheath of the femoral vessel made it impossible to complete the Basset type of gland removal. In a few instances the glands were removed only on the side where the cancer developed. All in all there were no serious operative difficulties, although great care had to be exercised when working close to the femoral and external iliac vessels. There were 2 postoperative deaths, one occurring twenty-four hours after a simple vulvectomy and the other occurring eight days after an operation in which the superficial removal of glands with vulvectomy was done. There were no operative deaths among the 16 patients on whom a double-sided Basset operation and vulvectomy were done. I think this favorable outcome is largely due to the fact that all the work was extraabdominal. Stoeckel and E. Kehrer have described a very extensive operation for gland removal in which they excised by laparotomy the iliac and hypogastric glands as well as the deep and superficial inguinal and femoral. Giesecke in his report from the Kiel clinic states that of the 15 cases where this technic was employed, 3 died from the operation (20 per cent). This is in my opinion too large a primary mortality to justify the procedure. I have hence retained the Basset technic especially as my five-year results are so very satisfactory.

The duration of the complete operation is often over two hours so that I have previously urged that it be done in two stages: one, the complete gland removal, and the other, the vulvectomy. Theoretically the gland removal should be done first and then the vulvectomy two weeks later, but where a large infected ulcer was present I have often found it more practical to clean up the vulva by a cautery excision first, proceeding with the Basset gland removal at a later time.

Regarding the technic of the vulvectomy, I wish only to stress the necessity of a complete removal of the leucoplakic skin to prevent the development of a new cancer and to warn against too radical an excision of the urethra where the cancer approaches this organ. The incontinence of urine where the urethra is removed is so distressing a

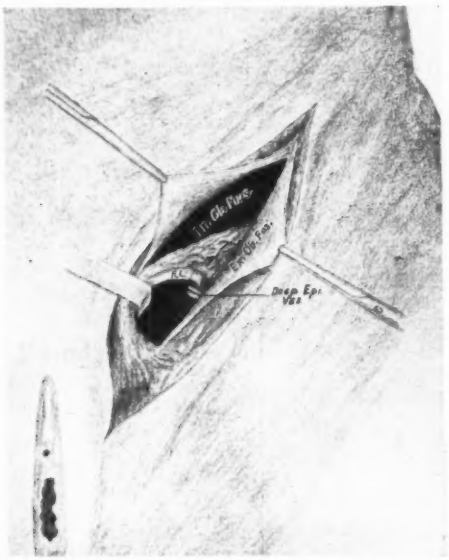


Fig. 18.—Basset's operation for lymph gland resection in carcinoma of the vulva (step 1). Incision over inguinal canal. Canal opened and round ligament isolated and lifted up. *R.L.*, round ligament; *Ex. Ob. Mus.*, external oblique muscle; *Ex. Ob. Fas.*, external oblique fascia; *Deep Epi. Ves.*, deep epigastric vessels.

complication that I would prefer to handle the urethral involvement in great part by the use of radium, since the urethra is very tolerant of radiation therapy.

The necessity of the removal of all the leucoplakic area is clearly demonstrated by the simultaneous appearance of multiple foci of cancer upon the vulval skin. Several cases of this sort were found in my series (Fig. 10). Even more is this shown by 3 cases in which a second new cancer developed some years later in another part of the vulva from a patch of leucoplakia that had not been removed. A brief record of these cases follows:

1. Ki. (Barnard, 492), sixty years, had a carcinoma of the left labium minus removed elsewhere by incomplete vulvectomy in 1913. In July, 1914, patient re-

turned with pronounced leucoplakic vulvitis over the right labia and entire perineum. At one point in the perineum a hard ulcer 1 by 2 cm. in diameter was noted that proved to be a new carcinoma.

2. G. (Barnard, 22009), thirty-nine years, had a small carcinoma of the upper left labia which was removed in combination with a double-sided Basset operation Sept. 23, 1920. At this time the entire labia were removed but the perineal skin did not appear involved in the leucoplakia and was not completely excised. On Sept. 12, 1923, an area of leucoplakia near the upper anal margin was noted in the center of which appeared an indurated ulcer 1 cm. in diameter. This was extensively excised with the surrounding deeper structure and proved to be a carcinoma. There has been no recurrence since that time. The last examination was made Jan. 30, 1929 (five and one-half years since the second operation).

3. Mrs. M. (Barnard, 22502), sixty years, had a carcinoma of the right labium majus, which was removed by vulvectomy and Basset gland removal, Nov. 24,

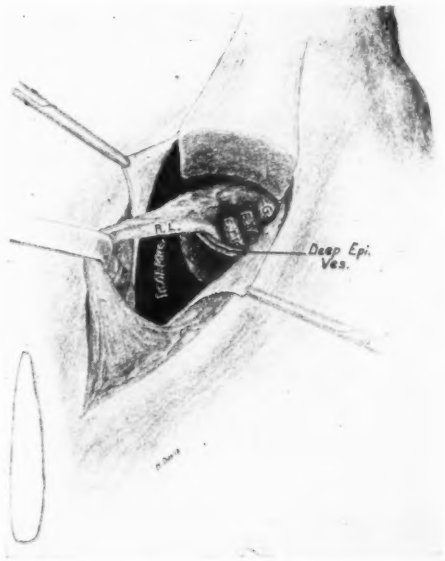


Fig. 19.—Basset's operation (step 2). Muscle retracted to expose internal iliac vessels and lymph glands to either side in iliac fossa. *G.*, gland; *E.I.A.*, external iliac artery; *E.I.V.*, external iliac vein; *R.L.*, round ligament; *Ex. Ob. Mus.*, external oblique muscle; *Deep Epi. Ves.*, deep epigastric vessels.

1920. No recurrence for over seven years. August 10, 1928, there was noted an area of leucoplakia, 1 cm. in diameter to the right of the urinary meatus, from which sprang a small papillary growth, that proved on section to be a carcinoma. Local excision. Patient died of influenza-pneumonia Dec. 8, 1928.

Cases of this kind have been noticed by others. H. R. Schmidt had two patients in whom over a period of from seven to eleven years new carcinomas developed on a leucoplakic basis at points far distant from the original tumor. It is important therefore in our operative procedures to remove all the leucoplakic skin and to consider any islands of leucoplakia that may subsequently become more prominent as potentially cancerous, removing them either by excision or cautery destruction.

Basset Technic.—Since the technic for removal of the tributary lymphatics described by Basset has proved so satisfactory as far as immediate and five-year results are concerned and since it has as yet not gained the recognition it deserves in the clinics of this country, a brief repetition of the important steps is in order.

1. An incision extending from a point 2 cm. internal to the anterior superior spine of the ilium, downward and inward, parallel to the inguinal canal, to 2 cm. below the tubercle of the pubis.

2. After pushing aside the skin and subcutaneous tissue, the aponeurosis of the external oblique muscle is incised parallel to the inguinal canal. The round ligament is thereby laid bare and then exposed along its entire course up to the inguinal ring. The peritoneum is pushed backward from the round ligament and the muscles of the abdominal wall retracted upward. In so doing, the lymph glands lying in the iliac fossa at either side of the external illiac vessels are exposed and can be

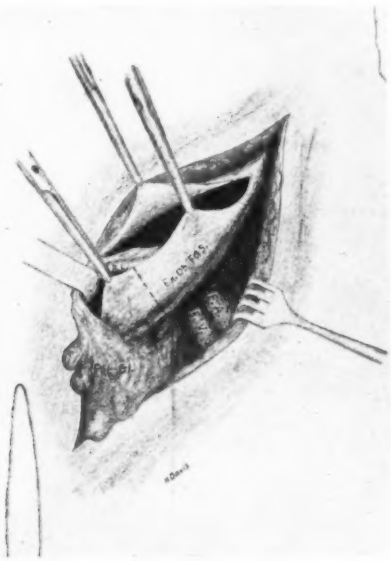


Fig. 20.—Basset's operation (step 3). Fascia drawn up and femoral lymphatics with surrounding fat dissected free from saphenous vein down to the femoral ring. The dotted line indicates where the cut is made through Poupart's ligament. *F. L. Gl.*, femoral lymph glands; *F.V.*, femoral vein; *F.A.*, femoral artery; *Ex. Ob. Fas.*, external oblique fascia.

removed in continuity with the round ligament which is ligated before being cut. Care should be taken at this point not to cut the important nerve trunks running parallel to the incision.

3. After clamps are placed on the fascia above the femoral ring, Poupart's ligament is drawn up and cut 1 cm. internal to the femoral vein. The two ends of the ligament are now drawn apart and the inferior epigastric vessels tied off closely to their origin from the iliac. The lymph gland of Cloquet, situated close to the femoral vein, is thus exposed and can readily be freed from its attachments. It is important, however, to retain its connection with the lymph channels running directly to the clitoris from this point. To do this will occasionally necessitate an additional skin incision downward to the region of Bartholin's gland. All the lymph glands in Scarpa's triangle should be dissected free. Thus the entire inguinal

and femoral lymph glands are laid bare in continuity with the tissues of the external genitals.

4. The closure of the inguinal wound can now be undertaken, first bringing the ends of Poupart's ligament together, and suturing them to the aponeurosis of the pectineus muscle, without, however, compressing the femoral vein. Now the transverse and oblique muscles of the abdominal wall are sutured to Poupart's ligament as in a hernia operation, and the aponeurosis of the external oblique muscle sutured over the top of the ligament.

The further steps of the operation consist of the removal of the primary growth of the vulva and need not be described in detail. A similar dissection of the lymph gland chain on the opposite side should precede the excision of the primary tumor.

Anesthesia.—The duration of the operation makes it desirable in these old women to get along with the minimum amount of general anesthesia. A good twilight to start with is of great advantage. A few

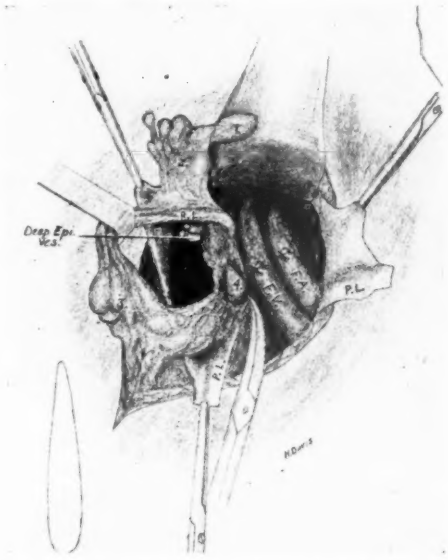


Fig. 21.—Basset's operation (step 4). Poupart's ligament with the lower flap of the external oblique fascia has been divided and drawn apart to expose Cloquet's gland just within the femoral ring. The inguinal lymphatics running along the round ligament have been dissected free. The deep epigastric vessels have been ligated and cut near their origin from the external iliac vessels. After resecting the round ligament and shelling out the gland of Cloquet, the whole mass is excised. The ends of Poupart's ligament are then sutured together and the oblique muscle fastened to it as in the operation for inguinal hernia. *P.L.*, Poupart's ligament; *F.A.*, femoral artery; *F.V.*, femoral vein; *R.L.*, round ligament; *Deep Epi. Ves.*, deep epigastric vessels; (*1*) deep inguinal gland (lateral to vessels); (*2*) inguinal glands along round ligament; (*3*) superficial femoral glands; (*4*) deep femoral gland or gland of Cloquet.

cases were done under spinal anesthesia. Local anesthesia can in most cases be used with good results and is I believe preferable, even if a small amount of general anesthesia has to be employed in addition.

Postoperative Care.—A retention catheter is usually inserted for the first forty-eight hours to avoid external manipulations during this time. If the perineoanal skin has been removed, it is well to put the patients on a diet that will keep the bowels from moving for a period of ten days. Of great importance is the question of dressings. Dry dressings

TABLE I. ANALYSIS OF FIVE-YEAR CASES OF VULVAL CANCER (1907-1923)

	TOTAL CASES	OPERATIVE DEATHS	DIED WITHIN 1 YEAR	DIED BETWEEN 1 AND 5 YEARS	DIED AFTER 5 YEARS	DIED OF OTHER CAUSES WITHIN 5 YEARS	CURED FOR 5 YEARS OR MORE	NOT TRACED	PERCENTAGE CURABILITY 5-YEAR AND ABSOLUTE
Palliative or refused treatment	4	–	1	1	–	–	0	2	0
X-ray or radium	15	–	11	2	–	–	0	2	0
Simple vulvectomy	6	1	3	–	–	–	–	2	0
Vulvectomy with superficial or incomplete gland removal	13	1	3	3	1	1 (4 yr. later)	4	1	30.7 (5-year) 23 (absolute)
Vulvectomy with complete double-sided Basset operation	11	0	1	1	2		9	0	81.8 (5-year) 63.6 (absolute)
Total cases	49	2	19	7	3	1	13	7	26.5 (5-year) 20.4 (absolute)

are applied for the first twenty-four hours but after that time there is so much wound secretion that it stagnates upon the dressings predisposing to wound infection and necrosis. I have, therefore, in recent years removed the dressings on the morning following the operation and kept the wound uncovered, protecting it from contact with the bedclothing by means of a wire frame in which is placed a lamp sufficient to keep the air warm and dry. In the evening dry dressings are placed over the wound and kept on during the night, to be removed on the following morning. Twice a day the wound is thoroughly irrigated with boric acid solution. Half strength tincture of iodine or 10 per cent silver nitrate or mercurochrome can be applied from time to time as indications arise. It is practically impossible to get primary wound healing in these cases but the necrosis and infection are markedly reduced by this method of treatment. In spite of frequent wound infection, I have had only one small hernia after the Basset operations, so that it does not appear that the cutting of Poupart's ligament is to be feared.

Five-Year Results.—The value of any method of treatment of cancer is based largely on the number of five-year cures obtained. If 7 out of the 49 cases in this group treated from 1906 to 1924 were not traced, this was largely due to the absence of a social service department in the earlier years of our hospital. In recent years every case is very closely followed up, reporting for reexamination every two to three months. The fate of the remaining 42 women is outlined in Tables I and II. From this it will be seen that no cures were obtained in any of the 15 cases treated with radium or x-ray; they all died within one year. It should however be said in fairness that only a few of these women had an early lesion. Equally unsuccessful were the cases in which a simple vulvectomy was done. None of the 6 cases passed the five-year period. Another group of 13 cases were those in which a superficial, one-sided or incomplete gland removal accompanied the vulvectomy. In one of these cases a Basset operation was attempted but owing to the invasion of a cancerous gland into the femoral sheath, this could not be carried out, hence it was included as an incomplete gland removal. Out of these 13 cases, four were free of recurrence longer than five years (30 per cent), but one died the following year of some bowel trouble. Striking were the results obtained in the 11 patients upon whom a Basset was done in addition to the vulvectomy. Of this number 9 remained free of recurrence longer than five years (81 per cent). Two women however developed a late recurrence, one at five and one-half years, from which she died and the other one at eight years. The latter after apparently complete removal of a small, local recurrence (new cancer?) died of an influenza pneumonia shortly afterward. Even so, we have left seven women free of recurrence at the present time, an absolute curability of 63.6 per cent with this type of operation.

TABLE II. SUMMARY OF BASSET OPERATIONS

	CASE	AGE CHILDREN	CLINICAL GROUP	MALIGNANCY INDEX	SYMTOMS COURSE	INVOLVEMENT	OPERATION	CANCER GLANDS	SUBSEQUENT RECORD
1	R. K. Barnard 15217	35 5-ch.	2	1	Leucovulvitis for years. Ulcer 8 months	Entire right labia. Ulcer 10 x 6 cm.	Vulvectomy and glands 10/12/15	None	Clinically cured Feb. 14, 1928 (13 years)
2	D. Barnard 17070	43 4-ch.	4	3	Trauma 1 year previous. Wass. 4+	Very large right side mass, many large glands	1/22/17 Basset. 2/5/17 Vulvectomy	Very many	Died recurrence Dec. 1917
3	G. Barnard 22009	39 0-ch.	1	2	Pruritus 1 year. Sore recently	Small ulcer 1 to 2 cm. left labia. Leucovulvitis	Radium (1200 mg.) 8/14/20. Basset and vulvectomy 9/23/20	None	Carcinoma at anal margin. Second operation 9/12/23. Clinically well. 1/30/29 (5 years)
4	M. Barnard 22502	60 5-ch.	1	2	No pruritus. Pimple on vulva 1 year	Cauliflower 3 cm. in right labia. Leucokraurosis	Vulvectomy and Basset 11/24/20	None	Small new carcinoma near urethra 8/10/28 removed. Died pneumonia 12/8/28 (8 years)
5	S. Barnard 23194	51 0-ch.	3	3	No pruritus. Lump on vulva 7 months	Rt. Bartholin gland tumor 4-5 cm. Glands large	Vulvectomy 4/30/21 Basset 7/20/21	Several	Recurrence (glands) 10/27/26 (5½ yr.) Died Dec., 1926
6	C. Barnard 27083	71 0-ch.	2	1	Tumor on vulva 5 months	Ulcer 4 cm. left labia. Leucoplakic vulvitis	Vulvectomy and Basset 7/3/23	Present (left side)	Clinically well 3/12/29 (5½ years)
7	S. Barnard 26664	73 12-ch.	2	2	Pruritus 2 years. Sore right side recently	Ulcer 5 cm. Prepuce and labia minora. Leucovulvitis	Vulvectomy and Basset 4/13/23	Tuberculosis. No carcinoma	Clinically well 3/1/29 (6 years)
8	P. Barnard 27141	46 3-ch.	1	2	Burning urination. Bleeding 2 months	Ulcer 2 to 3 cm. Vestibule around meatus urin.	Vulvectomy. Resect urethra. Basset 7/11/23	None	Clinically well 1/25/29 (5½ years)

TABLE II.—CONT'D

	CASE	AGE CHILDREN	CLINICAL GROUP	MALIGNANCY INDEX	SYMTOMS COURSE	INVOLVEMENT	OPERATION	CANCER GLANDS	SUBSEQUENT RECORD
9	T. Barnard 27968	63 0-ch.	1	2	Irritation near urethra 3 years	Ulcer 2 cm. Vestibule near meatus	Vulvectomy and Basset 11/14/23	None	Clinically well 2/28/29 (5 years)
10	E. (private)	74 7-ch.	3	3	Pruritus 1 year. Lump 3 months	Ulcer 8 cm. infiltration. Left labia. Leucovulvitis	Vulvectomy 4/7/23. Basset 4/21/23	Very many	Recurrence Feb., 1924. Died April, 1925 (1 year)
11	C. (private)	65 0-ch.	1	2	Pruritus 20 years. Lump 1 year ago. Radium 10 months. Excision 2 months	Recurrent. Ulcer 2 cm. right labia. Leucokraurosis	Vulvectomy 1/31/24. Basset 2/16/24	Present left side	Keratosis removed 12/2/25. Clinically well April, 1929 (5 years)
12	S. Barnard 32019	54 5-ch.	3	3	Pruritus and leucovulvitis	Tumor 7 x 7 cm. Left labia. Large inguinal glands	Vulvectomy 9/4/25. Basset 9/22/25	Very many	Recurrent. Died 10/2/27 (2 years)
13	M. E. Barnard 37534	55 0-ch.	3	1	Abscess left Barth. gland 13 yr. Lump 2 years	Tumor 8 x 6. Left Barth. gland involving rectum. Glands large	Vulvectomy and radium 12/16/27. Basset 12/21/27	Many	May 10, 1929 no recurrence (1½ years)
14	G. Barnard 38123	Colored 43 1-ch.	1	2	Pruritus 4 years X-ray for pruritus 5/14 to 6/29/28	Ulcer 1 cm. on leucoplakia of prepuce and labia minora	Vulvectomy 9/21/28. Basset 10/9/28	Present right side	No recurrence April, 1929 (6 months)
15	M. Barnes Hospital	Colored 45 1-ch.	1	1	Nodule on vulva cut 4 years ago. Frequent cautery. Did not heal	Ulcer 1 to 2 cm. left labium minus	Diagnostic excision 4/11/29. Vulvectomy and Basset 4/25/29	Examination not complete	Too recent
16	K. R. Barnard 36400	43 5-ch.	2	1	Pruritus several years	Ulcer 4 cm. left labia leucokraurosis	Vulvectomy 7/12/27. Basset 5/14/29	Examination not complete	Too recent

Unfortunately we have few statistics from other clinics with which to compare these results. In Bonn from 1912 to 1921, Schmidt reports only two out of 13 cases free of recurrence. Giesecke from the Kiel clinic reported 25 cases operated upon longer than five years ago, 10 of whom remained free of recurrence (40 per cent). Giesecke in 15 of these 25 cases employed the radical Stoeckel type of operation.

A more detailed statement concerning those patients operated upon by the Basset technic, given in Table II, will bring out other interesting points. The first 11 of the 16 cases were all operated upon more than five years ago. It will be noted that only 5 out of the 11 were in Group I, the very early cases, 3 were in Group II, 2 were in Group III and one was so far advanced that it was included in Group IV. From this it is evident that these cases have not been selected ones. It is further to be noted that every one of the 8 cases in Groups I and II remained free of recurrence for over five years, the only recurrence in this group was the one that occurred eight years after operation and is probably to be more rightly considered a new cancer. The malignancy index in these cases corresponds fairly closely to the clinical group.

The most convincing evidence of the value of the Basset operation is that in two of the cases that are still clinically cured, over five years ago there was found on microscopic examination carcinoma in the removed lymph glands. In Figs. 17-*A* and *B* is seen a microphotograph of one of these gland metastases.

SUMMARY AND CONCLUSIONS

Leucoplakic vulvitis appears usually in women shortly after the menopause. It may involve the entire vulva or appear in symmetrical or irregular patches. In over one-half of the cases there is an obliteration of the labial and preputial folds known as kraurosis. Pruritus of long standing is the most pronounced symptom. The disease is very rare in the negro race. In over one-half of the cases it leads to the development of carcinoma.

Further clinical and histologic studies tend to confirm the views previously expressed that the underlying cause of leucoplakic vulvitis is a loss of elasticity in the skin due in part to deficiency of ovarian hormones. This defect in the elastic structure leads to increased friability with resulting cracks and abrasions. Through these openings bacteria gain entrance and pruritus results. The scratching then increases the infection by providing new ports of entry. The chronic vulvitis thus produced leads to hyperplasias (keratosis, acanthosis) and later to atrophies (sclerosis, collagen formation, kraurosis).

The treatment of leucoplakic vulvitis, both on its own account and as a precancerous lesion, consists of excision of the affected vulval skin. The five-year results after such a vulvectomy are uniformly favorable and justify the discomforts attendant upon the operation.

These discomforts have been greatly reduced by two modifications in technic, the use of a vaginal flap over the perineum and the retention of a double anal bridge in cases of perianal involvement.

Cancer of the vulva is not a pathologic entity. There are 4 well defined types: (1) *epidermal,* springing from the labial, preputial or perineal skin, associated almost always with leucoplakic vulvitis; (2) *clitoris,* springing from that organ itself (not from the prepuce) a very rare and malignant form; (3) *vestibular,* arising from the vaginal introitus, usually springing from old syphilitic ulcers in relatively young persons; (4) *Bartholin gland,* also rare, usually after chronic Bartholinitis.

A division of the 76 cases in my series according to clinical involvement, showed that about 60 per cent were operable. A division of the cases according to the histologic malignancy index showed that this corresponded closely with the extent of the clinical involvement. It also showed that the cancers on a leucoplakic basis were relatively benign, whereas those springing from syphilitic ulcers, were very malignant.

The treatment of cancer of the vulva by radiotherapy has been very unsuccessful. Burns readily occur and retrogressions are few and temporary. Surgery is alone to be considered unless the patient's condition makes this impossible. Simple vulvectomies or superficial or one-sided gland dissections meet with a high percentage of recurrences. The double-sided Basset technic of gland removal together with vulvectomy is a safe operation followed by a high percentage of five-year cures (81.8 per cent in my series). Two cases with gland metastasis are among these cures. The vulvectomy must be complete in every leucoplakic case, since a new cancer may arise years later from a remaining island of leucoplakic skin.

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A CLINICAL AND ANATOMIC DESCRIPTION OF A NAEGELE PELVIS

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THE rarity of this type of pelvis, the beauty of our specimen, as well as certain interesting points in the clinical history of the patient from whom it was obtained, seem to justify its description.

Clinical Data.—The patient, B. T., Unit No. 17,583, had been under observation from 1917 to the time of her death in April, 1928. When first seen she was sixteen years of age, presented no striking external deformity, nor did anything in her previous history suggest the possibility of any unusual complication.

On her first admission, pelvic mensuration apparently showed a generally contracted funnel pelvis, with a distance of 7.25 cm. between the tubera ischii, with the head engaged in L.O.P. On March 17, 1917, she had a spontaneous labor lasting twenty-one hours, the occiput rotating into the hollow of the sacrum. The child weighed 2600 grams, presented a biparietal diameter of 8.25 cm., and at the end of the puerperium was discharged with its mother in good condition.

In December, 1918, a second spontaneous labor occurred. After a second stage of one hour and forty minutes, the child was expelled in L.O.A., when it was noted that only the lower portion of the pubic arch was occupied by the occiput. Again, the child was small, weighing 2890 grams and having a biparietal diameter of 8.75 cm.

On a ward visit shortly before her discharge, I saw the patient walking about and noted that her body had a "list" to the left. Upon inquiry, I was informed that she had a generally contracted pelvis and was convalescing from a second uneventful labor. As my curiosity was aroused, I examined her carefully, and eventually made the diagnosis of a Naegele pelvis, and dictated the following note: "On inspection there is a slight scoliosis in the lumbar region with its convexity to the left. There is slight asymmetry in the pelvic region, the left buttock appearing less well developed than the right. There is slight tilting of the pelvis, as the distance from the iliac crest to the floor measures 102 cm. on the right, and 101 cm. on the left side. The distance from the right anterior superior spine to the left posterior superior spine is 2 cm. greater than the corresponding measurement on the opposite side. Likewise, the distance from the spine of the last lumbar vertebra is 2.25 cm. greater to the right than to the left anterior superior spine, while there is a similar difference in the measurements between the tip of the sacrum and each of the ischial tuberosities.

"With the patient in lithotomy position, there is slight asymmetry of the pubic arch, as the left ischiopubic ramus extends outward at a sharper angle than the right. The symphysis pubis is vertical. On internal examination, the sacrum is felt throughout its entire extent, the promontory is readily palpable, and the diagonal conjugate measures 11.5 cm. The entire linea terminalis can be palpated. On the left it extends obliquely backward in a straight line and terminates about 1 cm. to the left of the body of the first sacral vertebra. On the right side the terminal line presents the usual concavity and terminates posteriorly 2.5 cm. to the right of the body of the first sacral vertebra. It is impossible to ascertain the condition of the sacroiliac joints, but there is clearly a radical difference between the two sides. Both ischial spines are readily felt, and the left one approaches the sacral

margin closer than the right. In general, it may be said that the pelvis is Naegele in character, and that the superior strait roughly corresponds to the accompanying sketch. (Not reproduced.) While the symphysis pubis does not appear asymmetrical, the conjugata vera extends obliquely to the left, the sacral promontory lying several centimeters to the left of a line extending sagittally backward from the top of the symphysis."

Fig. 1 shows the front and back views of the patient, while Fig. 2 is a reproduction of the x-ray print which was taken at that time, and which confirmed the diagnosis.

Following this, the patient was not seen again until 1926, although she stated that during the intervening period (1920, 1921, and 1923) she had had three

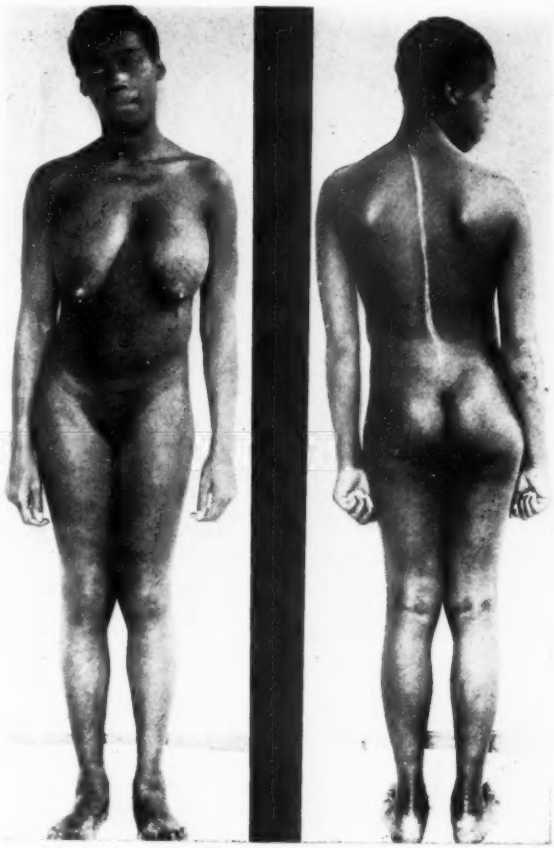

Fig. 1.—Front and rear views of patient. Note tilt to left of torso.

spontaneous labors at home under the care of a midwife, and that all of the children were small. On April 18, 1926, her sixth pregnancy terminated spontaneously at home under the care of our Out-Patient Service. At that time the child presented in R.O.A. and was born uneventfully after a labor of eight hours. Again, it was small, weighing 2900 grams, with a biparietal diameter of 8 cm.

The patient was next seen in January, 1928, when she applied to the Prenatal Clinic for care in her approaching seventh delivery. The assistant in charge, being led astray by the history of repeated spontaneous labors, failed to look up the previous histories and thus overlooked the existence of the Naegele pelvis. A

diagnosis of a moderately generally contracted funnel pelvis having been made, it was arranged that the patient should be delivered in her own home by the Out-Patient Service. She fell into labor on March 17, 1928, with the child in R.O.A. Seventeen hours later the cervix was found to be fully dilated, with the head at the level of the spines. As no advance had occurred at the end of two more hours, the assistant decided to apply forceps. As he experienced difficulty in doing so, he gave up the attempt, and extracted a live child after what he termed an easy version. The placenta did not separate spontaneously, and, as several attempts at Credé expression were ineffectual, manual removal was resorted to one hour after delivery. The patient was watched for a further hour, and was left in apparently excellent condition. The child was large, weighing 3400 grams and having a biparietal diameter of 9.5 cm.

Some hours later, word was sent to the Clinic that the patient was not doing well, and, when seen by the externe, she was found to be so seriously ill, with rapid pulse and painful and distended abdomen, that she was at once brought to the clinic. I saw her shortly after admission, made a diagnosis of traumatic rupture of the

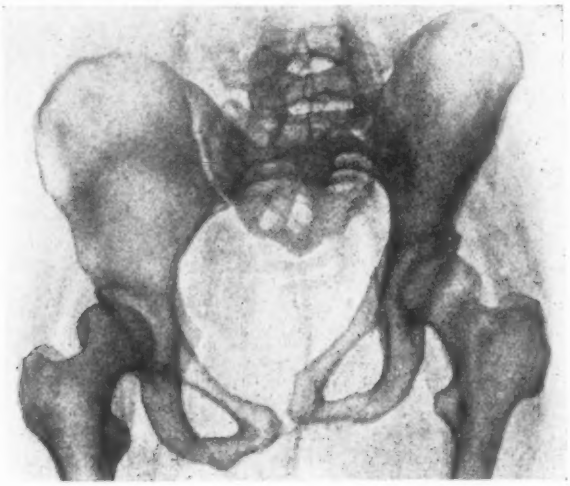

Fig. 2.—Reconstruction of x-ray of patient.

uterus with intraabdominal bleeding, and operated as soon as the necessary preparations could be made. On opening the abdomen large quantities of free blood were present, and the uterus was found to be ruptured through the right and anterior portion of the lower segment. Supravaginal hysterectomy was done and the patient left the table in good condition. On the second day bronchopneumonia was diagnosed, and the temperature remained elevated until death occurred on the twenty-fifth day. At autopsy it was found that the patient had a tuberculous pneumonia, while a minor infective process had developed in the pelvic cavity. The entire pelvis was then removed, together with the last two lumbar vertebrae, and the upper ends of the femora.

To summarize, we had to deal with a patient having a typical Naegele pelvis, through which she had six spontaneous labors with small children, and who died after the operative delivery of a seventh child. In the first three of the four labors, which we conducted, the largest child weighed 2900 grams and had a biparietal diameter of 8.75 cm., while in

the last labor the child was much larger and weighed 3400 grams with a biparietal diameter of 9.5 cm. Upon studying the outlines and dimension of the pelvis, as shown in Figs. 3 to 5, it is apparent how spontaneous labor had occurred with the small children, and how it became impossible when the last child had attained more than average proportions.

Furthermore, our records show that the child presented in L.O.P., L.O.A., and R.O.A., in the first, second, and sixth labors respectively. Consideration of Fig. 3 shows that engagement could have occurred with the head in L.O.P. or R.O.A., as in either presentation its long diameter would occupy the left oblique diameter of the superior strait, which measures 11 cm., while the small biparietal diameter would accommodate itself, after some moulding, to the right oblique diameter of 8.4 cm. On the other hand, it does not appear probable that a child presenting in L.O.A. could undergo engagement. Consequently, as the history states that in the second labor the occiput was delivered anteriorly, it must be assumed that when labor set in, the occiput, which had originally rested upon the anterior portion of the slanting left linea terminalis, had slipped forward and eventually became engaged in R.O.A.

The tragic end of the last labor must be attributed to the carelessness of the assistant concerned, and demonstrates how difficult it is to conduct an ideal service. Had he taken the trouble to go over the previous histories, he would have found that he had to deal with an unusual pelvis, and automatically would have sent the patient into the clinic, where the disproportion would have been recognized and properly treated. Excuse for him may be found in the fact that the patient had already gone through six spontaneous labors, three being in the hands of a midwife; so that, in the absence of gross and striking abnormality, the presumption would be in favor of a similar outcome at the seventh delivery.

Finally, before passing on to a description of the pelvis, it should be mentioned that the patient walked without a limp. It is true that careful inspection did reveal an abnormal bodily habitus, but it was so slight as to escape detection by any but an acute observer. Furthermore, and especially in connection with the etiology of the deformity, stress should be laid upon the fact that there was nothing in the history to indicate that the patient had at any time suffered from inflammatory bone disease. After her death her husband and elder sister were carefully questioned on this point, and both stated that she had at no time been bedridden, nor had she ever complained of any disturbance in locomotion; on the contrary, they claimed that she was "light upon her feet" and quick in all her movements. Finally, careful inspection of Fig. 1 fails to reveal any trace of scars about the thighs,

buttocks or groins, which might have directed attention to a preexisting inflammatory process about the sacroiliac joint.

Description of Pelvis.—Figs. 3, 4 and 5 make it clear that we have to deal with a typical Naegele or obliquely ovate pelvis, in which the left sacroiliac joint has been obliterated, a considerable part of the left ala of the sacrum has disappeared, and what remains of it has become firmly synostosed with the left innominate bone.

The extent of the obliquity is shown by the following measurements:

Left anterior superior to right posterior superior spine 15.75 cm.
Right anterior superior to left posterior superior spine 19.75 cm.
Tip of spinous process of first sacral vertebra to left anterior superior spine 13.5 cm.
Tip of spinous process of first sacral vertebra to right anterior superior spine 16.0 cm.
Center of promontory to right sacroiliac joint 5 cm.
Center of promontory to left sacroiliac joint 3 cm.
Center of promontory to right ileopectineal eminence 9.3 cm.

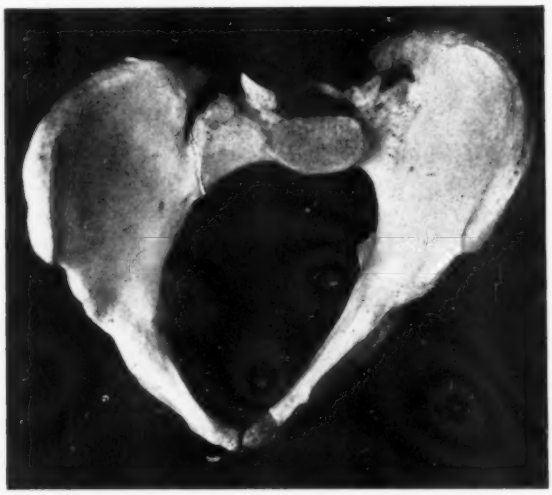

Fig. 3.—Naegele pelvis, superior strait x ⅓.

Center of promontory to left ileopectineal eminence 6.0 cm.
Tip of sacrum to right ischial spine 8.1 cm.
Tip of sacrum to left ischial spine 5.7 cm.

The entire pelvis is somewhat smaller than usual, as is shown by the following measurements: Distance between anterior superior spines 18 cm.; between iliac crests 20.5 cm., and Baudelocque diameter 18.75 cm. At first glance, it might appear that the left innominate bone is somewhat atrophic as compared with the right, but mensuration shows that such is not the case, as the two sides present practically identical measurements which in no place differ by more than one-half centimeter. Thus, the length of the iliac crests, as measured between the anterior and posterior spines by a pelvimeter, is 14 cm. on the right and 13.5 cm. on the left side. Likewise, the distance between the ends of the pubic bone and the corresponding anterior superior spine of the ilium is 17.2 cm. on the right, and 17.5 cm. on the left side. Finally, the height of the pelvis, as measured from the center of the tuber ischii to the highest point of the corresponding iliac crest, is 18.5 cm. on the right and 18.75 cm. on the left side.

Fig. 3, which represents the superior strait, shows the characteristic obliquely ovate form, and illustrates a number of features which are familiar to those acquainted with the Naegele pelvis. In the first place the ileopectineal line on the right side presents an exaggeration of the normal curvature, as contrasted with its almost straight course on the abnormal side. As a consequence, the symphysis pubis lies eccentrically, so that the anterior termination of the conjugata vera is formed by the tip of the right pubic bone. It will also be noticed that while the terminal length is practically identical on the two sides (right 18.4 and left 18.6 cm.), the dimensions of its component parts differ considerably. Thus, on the right side the pubic, iliac, and sacral portions measure 6.5, 5.8, and 6 cm. respectively, as compared with 6.5, 5.1 and 7 cm. on the abnormal side. In other words, while the pubic portions are identical on both sides, the iliac portion is 7 mm. shorter and the sacral portion 10 mm. longer on the abnormal side. This is in accordance with the observations of Breus and Kolisko, who claim that it is the general rule, and is due to the fact that, owing to the absence of the articular facies of the ilium, the growth of the iliac portion of the terminal length is defective, with the result

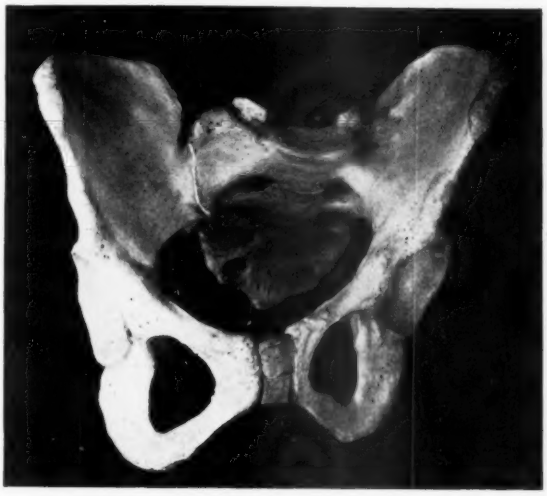

Fig. 4.—Naegele pelvis, front view x ⅓.

that the ala of the sacrum does not become displaced backward during the growth of the pelvis, so that the sacral portion of the terminal length remains longer than usual. This observation is also confirmed by reference to Fig. 5, which shows that the posterior extremity of the iliac crest projects 7 millimeters further beyond the posterior surface of the sacrum on the abnormal than on the normal side.

Fig. 3 shows the distortion of the superior strait, whose usual diameters present the following measurements: conjugata vera 11.4 cm., transverse 9.5 cm., right oblique 8.4 cm., and left oblique 11 cm. It will be noticed that the conjugata vera extends obliquely backward from the inner surface of the tip of the right pubic bone to the center of the promontory of the sacrum, whereas a line drawn directly backward from its anterior termination practically bisects the right sacral ala.

Fig. 4 shows that the sacrum measures 10 centimeters from promontory to tip, and that its long axis is oblique instead of vertical, with its upper end approaching the left, and its lower end the right side of the pelvis. The most impressive feature of this aspect of the pelvis, however, consists in the radical changes which have taken

place in the region of the left sacroiliac joint, which has become entirely obliterated, while the left sacral ala is only a fraction as broad as the right, the destruction being much more pronounced in its anterior portion.

It will further be noticed that where fusion has occurred, the surface of the bone presents a burnished appearance, almost as if it had been artificially polished, and gives no suggestion that the ankylosis had followed an inflammatory process. Furthermore, it will be noticed that on the normal side the bodies of three sacral vertebrae take part in the formation of the joint, whereas on the fused side only two are involved.

In connection with the sacroiliac joints, consideration of Figs. 3 and 4 will show that on the normal side the upper margin of the articular facies of the ilium is in contact with a similar articular surface of the sacrum for a distance of 3 centimeters, while beyond it there is a free portion which extends backward for a distance of 17 millimeters. On the abnormal side there is no joint surface, but the sacrum

Fig. 5.—Naegele pelvis, inferior strait x ⅓.

and ilium have become intimately fused for a distance of 4.7 cm. It may also be noticed at the extreme posterior end of the line of fusion that there is a roughened elevation of porous bone (10 by 6 by 3 mm.), which to my mind constitutes the only evidence that can be adduced in support of the supposition that an ostitic process had ever existed in this locality.

On casual inspection of Fig. 4, it might appear that the pubic arch is asymmetrical, with the left ischiopubic ramus shorter than the right. Mensuration, however, shows that such is not the case, as there is a difference of only 2 millimeters in the length of the two rami. There also appears to be a marked difference between the two acetabula, and it is evident that the left one is directed more anteriorly than the right. On the other hand, the apparently greater depth of the posterior aspect of the articular surface of the left acetabulum has no existence in fact, as mensuration shows that it is actually shallower than on the right side (2.4 to 2.7 cm.).

Fig. 5 gives a good idea of the distortion of the inferior strait, except that it seems to show that the distance between the ischial spines is shorter than between

the tubera ischii; whereas in reality the former measures 8.3 as compared with 8 cm. Attention has already been directed to the greater extent to which the posterior end of the left iliac crest projects beyond the posterior surface of the sacrum, as well as to the views of Breus and Kolisko concerning its incidence and significance.

As was previously stated, the last two lumbar vertebrae were removed with the specimen, and when they are placed in position it appears that a slight scoliosis must have existed during life, with its convexity low down on the left side. As will be pointed out in the next section, the scoliosis is less pronounced than would have been expected. That a pronounced disturbance in the statics of the pelvis had existed during life is shown by the status of the two superior articular facets of the first sacral vertebrae. Fig. 3 shows that their attitude is not altered, as indicated by their inclination to the midline, but inspection reveals that they differ materially both in shape and size. Thus, the right articular facet is oval in shape, with its long diameter extending transversely, and measures 20 by 13 millimeters; while the left facet is roughly quadrilateral in outline, with its long diameter vertical, and measures only 15 by 13 millimeters. From this it would appear that better mechanical conditions had existed on the right than on the left side, which may have had an important bearing upon the unimpaired locomotion of the patient.

Implications.—In Naegele's original monograph, which appeared ninety years ago, the description of the morphology of the obliquely ovate pelvis was so masterly that nothing has since been added to it. As is well known, Naegele attributed the deformity to a congenital defect involving one ala of the sacrum with resulting imperfect development of the sacral portion of the sacroiliac joint. Furthermore, when the individual began to move about, the body weight would in great part be transmitted to the femur on the affected side, with the result that unusual pressure would be exerted upon the abnormal joint, and that the irritation induced thereby would eventually lead to ankylosis. His original publication was followed by a considerable literature, and all of the earlier contributions were confirmatory of his point of view. Indeed, it was not until 1861 that any scepticism developed, when Thomas of Leyden pointed out that in at least a certain proportion of obliquely ovate pelves the essential feature lay in the destruction and subsequent fusion of an originally normal sacrum as the result of inflammatory disease, rather than in a primary defect in development.

Since then the discussion has continued, and reached its culmination in 1900, when Breus and Kolisko in their monumental work on deformed pelves stated that the condition is always the result of inflammatory disease, whose existence can generally be elicited from the history of the patient, and particularly from the presence upon the external surface of her body of cicatrices which indubitably indicate that such disease had existed.

In the second volume of their great work, 203 pages are devoted to the consideration of "Ostitic and Synostitic Pelves," and 147 of them are concerned entirely with the Naegele pelvis. In the first part of their study it is clearly shown that all sorts of deformity may follow

tubereulous or other inflammatory destruction about the sacroiliac joint, which when extreme may eventuate in the production of the characteristic Naegele deformity. In many specimens the inflammatory nature of the condition is demonstrated by the presence of irregularly shaped deposits of callus, which admit of no other interpretation, and frequently is still further confirmed by the presence of cicatrices which mark the location of old sinus tracts. Indeed, Breus and Kolisko go so far as to believe that all examples of the so-called Naegele pelvis are ostitic in origin and state that in their extensive studies they could find no evidence that the congenital defect described by Naegele is ever concerned in its production. Furthermore, they hold in the rare instances in which such developmental defects do occur that they uniformly give rise to pelves of totally different character.

After carefully studying the pelvis here described, it occurred to me that it might be of interest to attempt to ascertain in how far it serves to support the contentions of Breus and Kolisko. At this point, I think it only fair to admit that my studies have led to no definitive conclusions, and that the most that can be claimed from them is that they tend to indicate in a certain proportion of cases, at least, that a final conclusion is not so easily reached as one might gather from their sweeping conclusions.

In the first place, inspection of this specimen does not show any evident signs of the existence of a previous inflammatory process, and the only thing which could possibly be suggested in support of such a view is the presence of a small irregularly rounded elevation made up of porous bone at the upper and posterior margin of the anchylosed area. This, however, cannot be regarded as convincing, since areas of similar consistency are frequently noted in otherwise normal pelves.

The second point opposed to the inflammatory etiology of the deformity is afforded by the history and inspection of the patient. As has already been indicated she walked without a limp, and after her death her husband stated that she had never mentioned that she had suffered from any form of bone disease during childhood. Furthermore, her older sister confirmed these statements, and stated that the patient had learned to walk at the usual age, had never limped, nor complained of any trouble in locomotion, but, on the contrary, had always been very light on her feet. Such a history is of considerable importance, as it is scarcely conceivable that an inflammatory lesion, sufficiently severe to bring about the extensive destruction of tissue necessary to produce the deformity, could have existed without giving rise to clinical symptoms or without necessitating a prolonged stay in bed.

With this point in mind, the exterior of the body was carefully examined at the time of autopsy with a view to detecting any cicatrices, which might have followed an ostitic process, but none were found. Furthermore, inspection of Fig. 1, which reproduces the photograph taken after the second labor, shows that none were discoverable in 1918.

Still more conclusive negative evidence is afforded by Fig. 6, which represents an x-ray picture of the upper portion of the region involved, which was kindly taken by Dr. Eben C. Hill, Lecturer in Roentgenological Anatomy. This type of investigation was adopted in the hope that the bony architecture might make it possible to draw some conclusion as to what had previously taken place in that locality. The figure clearly shows that the bony fibers extend continuously from the sacrum into the adjacent ilium, and pursue so regular a course that Dr. Hill does not consider their arrangement compatible with a previous inflammatory process, as he holds that had the anchylosis occurred subsequent to it the course of the fibers must have exhibited some interruption

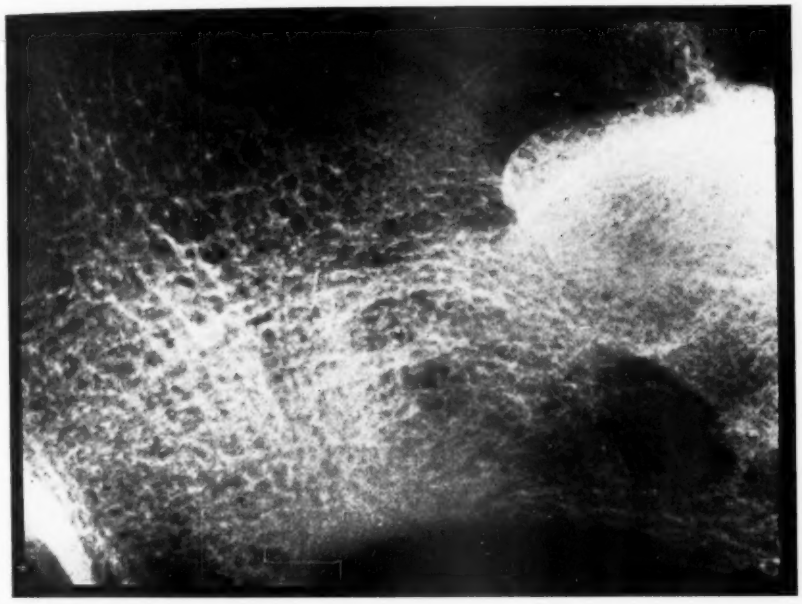

Fig. 6.—X-ray showing bony architecture of left sacroiliac region.

or irregularity. Possibly additional information might have been elicited had sections been made through the region involved, but the specimen was so valuable that I hesitated to sacrifice it for scientific purposes.

Summing up our findings in this regard, it seems safe to say from the history of the patient, the absence of cicatrices, the gross appearance of the specimen, as well as from the x-ray findings, that it seems impossible that the patient had suffered from a serious inflammatory bone lesion after birth, and consequently it seems likely that the deformity must be attributed to conditions which came into play during antenatal life—in other words, that it is congenital. On the other hand, our knowledge is unfortunately too defective to permit even a guess as to its nature, so that I shall content myself by stating that the contentions of

Breus and Kolisko do not seem to apply to our specimen, and that it is probable that their generalizations must share the fate of all exclusive statements—namely, that while they are usually correct, they do not necessarily apply to the individual case.

Attention has already been directed to the fact that the bearer of this pelvis, in common with others mentioned in the literature, did not limp, and the question arises as to how so striking a deformity is compatible with a normal gait. Breus and Kolisko have devoted considerable attention to the problem, and believe that its solution is to be found in the fact that the scoliosis which develops in the lumbar region is compensated for by a second curve higher up in the vertebral column, with its convexity in the opposite direction, with the result that the symphysis pubis occupies the midline of the body, while the body weight instead of being transmitted directly to the promontory of the sacrum comes to be transmitted along a vertical line extending somewhere between the promontory and the normal sacroiliac joint. In this way, the body weight will be transmitted with almost equal force to the heads of the two femora, and consequently, the patient will limp but slightly, if at all.

Do such considerations apply to this pelvis? Reverting to Fig. 1, it is seen that the vulva, and inferentially the symphysis pubis, occupies the midline of the body, but that the entire torso is somewhat tilted toward the left. On inspecting the dorsal aspect of the patient, it is seen that the lumbar scoliosis is scarcely apparent, and that the vertebral column above it, instead of presenting a compensatory scoliosis as postulated by Breus and Kolisko, continues to diverge toward the left up to the last cervical vertebra, which according to their contention should have led to an unequal distribution of the body weight, and consequently to a limp. Yet it has been repeatedly stated that our patient did not limp.

The only explanation which I can offer for this apparent contradiction of terms is possibly afforded by the development of a compensatory process in the cervical portion of the vertebral column. Inspection of the frontal aspect of the patient, as depicted in Fig. 1, shows that the head and neck are so deflected toward the right side that a straight line drawn through the heels and the symphysis pubis and extending through the head, passes through the center of the left eye instead of through the center of the forehead. Whether such a habitus would suffice to restore the statics of the body to essentially normal conditions, I am unable to state. If it did, it would be contrary to the conditions laid down by Breus and Kolisko, and would afford another demonstration that their conclusions are not infallible.

IMPORTANT PROCEDURES IN THE CONSERVATIVE TREATMENT OF ECLAMPSIA

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THE good results given by the widely separated methods of the conservative treatment of eclampsia, that is, the use of elimination by Tweedy and the use of sedatives by Stroganoff, indicate that the maternal organism will recover if the disease has not lasted too long and the damage has not been too great. The favorable and unfavorable reports of various clinics based on one or the other methods suggest that each case must be individualized and that both experience and judgment are necessary. Furthermore, obstetricians have recognized as a result of the high maternal mortality that mild cases if treated radically will show an increase in the mortality rate, and severe cases treated conservatively will continue to show a definite mortality if early death of the fetus does not take place or delivery occur. As a result, many have taken the good points of each treatment and by combining them and determining the type of case are beginning to get still more favorable results. They have also realized that certain severe cases must be handled by early delivery. The difficulty still persists, however, in that it is usually impossible to decide as to the severity of the case before too much damage may have occurred.

In our studies of the toxemias of pregnancy we have found that there are a mass of results reported, but that there is no uniformity. Therefore, from the beginning we have been collecting as much data on each case as time permitted and have constantly increased the variety of examination as our accumulated material gave fresh ideas or required additional confirmation. Our results indicate the need for certain specific treatment the use of which enables us to give a prognosis early enough to be of value. Much of this data is not included in this paper but will furnish the basis of an additional report.

Our treatment can be summarized as follows:

1. $MgSO_4$ in 25 per cent solution is given intramuscularly to control convulsions. On admission we inject 10 c.c. and give 5 c.c. after each convulsion until controlled. Our average amount over a period of five years has been 19 c.c. with a maximum of 50 c.c. in only one case. In coma no $MgSO_4$ is used, for we believe that its only action, if given intramuscularly, is as a sedative. If given intravenously it does decrease intracranial pressure, but its depressant action on the respiration and the heart are so marked that they contraindicate its use. Dorsett has given intramuscularly from 15 c.c. to 200 c.c. depending on the severity of the case. In three cases he gave 200 c.c. per twenty-four hours. We attribute our success with the

small dose in not only controlling the convulsion but also preventing their further occurrence to the use of intravenous glucose.

2. Believing that absorption from the alimentary tract is an important factor, we give a colonic irrigation and in addition usually wash out the stomach and leave 60 c.c. of a saturated solution of $MgSO_4$ in it.

3. Our next, and most important procedure is to inject 1000 c.c. of a 20 per cent glucose solution intravenously over a period of thirty to fifty minutes, two, three, or even four times daily, depending on the severity of the case.

4. Usually after twenty-four hours, the stomach will empty itself as evidenced by failure to recover injected solution, and then we inject 5 per cent Karo syrup water beginning with 50 c.c. and increasing hourly up to the patient's tolerance which may be as much as 300 c.c. per hour. This is continued until the patient is conscious and able to take our eclamptic diet, which consists of fruit and fruit juices.

In Table I, we list data from a number of cases of eclampsia giving the findings (1) on admission, (2) at the time of greatest blood dilution, and (3) at discharge (which is at least three weeks postpartum). All of our cases on admission had a blood concentration as evidenced by high hemoglobin, cell volume percentage, and serum protein percentage. Case 2734 admitted and treated as a preeclamptic had blood findings which were normal for her period of gestation but during labor she had convulsions and blood taken at this time was concentrated.

Shortly after delivery, it has been demonstrated by numerous investigators, Zangemeister, Eckelt, Dienst, Stander and Tyler, Plass and Bogert, Thompson, and de Wesselow that a blood dilution occurs in which the cell volume, hemoglobin, protein, specific gravity, and certain of the inorganic constituents all take part. Our work indicates that this dilution occurs within twenty-four hours postpartum or after death of the fetus. It is during this period of blood dilution, with its accompanying physicochemical changes, that the greatest clinical improvement, greatest diuresis, and greatest weight loss take place. We find that the cell volume percentage drops 15 to 25 per cent while the protein decreases 25 to 35 per cent. Furthermore, the serum proteins return to normal within two weeks but the cell volume percentage and hemoglobin at the time of discharge, which is at least three weeks, have not returned to normal.

In the normal individual the urine represents approximately 90 to 100 per cent of the fluid ingested (Atwater); but in normal pregnancy it represents only 50 to 60 per cent (Slemons). Thus with such a high positive water balance required for the growing fetus, it is evident that any disturbance may have serious results, which may be edema or dehydration, depending on whether the balance is positive or negative. After delivery a diuresis occurs in which the urine represents 60 to 80 per cent of the water intake. Slemons reports that in a case in which the fetus was dead, the urine represented 93 per cent of the fluid intake. In the toxemic patient after delivery, the urine represents 90

to 100 per cent, and if the patient is edematous, it actually exceeds the intake. It is therefore evident that the diuresis is a physiologic phenomenon occurring only after delivery or death of the fetus and since its appearance is so intimately associated with clinical improvement, we consider its production of primary importance. Tables II and III are representative of typical changes in the blood and urine in eclampsia, especially after delivery; and Table IV of changes both before and after. In a number of cases we have succeeded in lowering the serum

TABLE I

NUMBER		DATE	HEMOGLOBIN	CELL VOLUME PER CENT	SERUM PROTEIN PER CENT	WEIGHT KILO.
F. F.	1*	7/18/27	113	46.4	6	77.7
11738	2	7/19/27	102	34	3.82	
	3	8/17/27	81	40	6.35	62.3
E. D.	1	9/ 6/27	86	39	5.92	
174	2	9/ 6/27	98	41	5.56	
	3	9/20/27	76	35	5.8	
E. B.	1	10/16/27	91	43	5.03	70.2
440	2	10/21/27	65	30.8	4.42	
	3	10/25/27	74	32	5.12	
L. B.	1	11/24/27	83	40	6.81	
715	2	11/29/27	66	35	6	
	3	12/ 7/27	70	36	5.85	
N. C.	1	2/16/28	101	42	8.42	79
1332	2	2/17/28	72	28.8	4.93	
	3	2/29/28	82	30	7.5	67
M. W.	1	4/10/28	111	42	6.4	166
1760	2	4/12/28	58	27	4.43	
	3	5/ 3/28	83	36	7.23	116
T. H.	1	5/15/28	91	37	6.54	
1992	2	5/15/28	70	28	5.17	
	3	5/24/28	59	26	6.4	
McC.	1	5/24/28	100	44	6.42	
2062	3	6/ 1/28	75	35	6.45	
W. P.	1	8/12/28	63	34	5.13	71.2
2734	a	8/18/28	105	55	5.6	
	2	8/20/28	66	32	4.28	
	3	9/ 1/28	85	34	6.45	60
E. A.	1	10/18/28	85	45	5.55	75
3380	b	10/19/28	119	49	5.52	
	2	10/20/28	105	41	4.15	
	3	11/ 5/28	98	35	6.26	
W. W.	1	10/25/28		49	5.83	65
3437	2	10/30/28		32	4.8	58
	3	11/ 5/28		50	6.88	56.8
F. S.	1	12/ 6/28	117	42	6.43	69.6
3779	2	12/ 8/28	90	36	5.45	
	3	12/10/28	111	38	6.73	
L. W.	1	1/16/29	121	42	5.86	72
4129	2	1/21/29	83	31	4.84	
	3	2/ 8/29	100	40	6.36	49.5
M. B.	1	4/ 2/29	105	40	7.47	69
4640	2	4/ 6/29	77	24	5.64	62
	3	4/22/29	64	27	6.92	

*1. Admission; 2. Greatest Dilution; 3. Discharge; a. Convulsion; b. Aftertreatment.

protein concentration before delivery but we have never succeeded in producing the typical diuresis of 4000 c.c. or more except after delivery or death of the fetus. Table V demonstrates that identical changes can occur before delivery. In this case no fetal movements, were noticed by the mother after July 20, and it is a fair assumption that the fetus died on that day. This is supported by the fact that the urine increased steadily from 400 c.c. on the twentieth, to 2400 c.c. on the twenty-first, and reached a maximum of 6600 c.c. on the twenty-third, and then slowly dropped. No diuresis occurred after delivery on the twenty-seventh.

Our treatment differs from that described by other clinics in that we use large amounts of hypertonic glucose solution and it is to this that we ascribe not only our favorable results but also our ability to control the convulsion with small amounts of $MgSO_4$. Hypertonic glucose solution injected intravenously reduces intracranial pressure, which is usually markedly increased in eclampsia. (Zangemeister, Thies.) Hypertonic salt solution was first used by neurologic surgeons to lower the intracranial pressure but was discarded in favor of glucose because the latter is just as efficient, has no terminal increase in intracranial pressure as NaCl or Ringers has (Peet, Weed and McKibben, and Sachs and Belcher), and can be repeated more frequently because its end-products are CO_2 and water. A 1 per cent solution of $MgSO_4$ is recommended for intravenous injection in nephritic uremia to control the convulsions. It has a dehydrating effect on the brain (Blackfan). We attempted this in one case but stopped the injection because of the effect on the respiration.

It is the general belief that glucose solution if injected intravenously is burned, stored as glycogen and polymerized (Sansum and Woodyatt, and Erlanger and Woodyatt), and if the amount is greater than can be removed by these mechanisms, the excess is excreted in the urine, resulting in a polyuria. Therefore, our purpose was to give enough glucose to produce a glycosuria, thus hoping to initiate a diuresis. We found that in the normal individual 500 c.c. of a 20 per cent solution of glucose (100 gm.) if given over a period of sixty to ninety minutes will not produce a glycosuria; but if given in thirty to fifty minutes will result in 10 to 30 gm. being excreted in the urine. If 200 gm. of glucose are given in thirty to fifty minutes, from 70 to 100 or more grams will be excreted in the urine. We give the eclamptic patient 1000 c.c. of a 20 per cent glucose solution (200 gm.) intravenously over a period of thirty to fifty minutes, two, three, and sometimes four times daily. Twenty-four-hour urine examinations have shown that comparatively little or no glucose is excreted in the urine. In Table VI, we have tabulated those pateints in whom we have twenty-four-hour urines and in only three cases was more than 100 gm. of glucose excreted in the urine per day. Two patients, Cases 3437 and 3380, received injections of

800 c.c. of a 30 per cent instead of 1000 c.c. of a 20 per cent solution, and the excessive glycosuria is apparently due to too great a strain on the tolerance which is apparently approximately 200 gm. We have decreased the amount of 30 per cent to 700 c.c., for although 30 per cent produces a more marked diuresis than 20 per cent, more sugar is excreted in the urine and apparently less toxic material excreted; for it seemed to us that these two cases did not respond as well to injections of 30 per cent as they did to 20 per cent. The glycosuria in the majority of the cases varied from none up to 50 gm. per twenty-four hours. There is no apparent relation between tolerance and weight or edema.

The urine output was increased in all cases to whom the treatment as detailed was given; but it was not due to the glycosuria for either there was none or at most of only a moderate degree. In the latter event the excretion of glucose is so small in proportion to the urine that it is evident that other factors are involved. Once a polyuria has been produced in eclampsia by glucose, it usually continues. This may be due to changes produced by the glucose in the cell or the cell membrane which are changed in pregnancy.

The blood pressure undoubtedly plays a part in the diuresis. Experimentally it has been proved that the urine varies directly as the blood pressure, therefore, in the eclamptics one would expect large amounts of urine but actually an oliguria or anuria exists. The fact that a diuresis can be established so rapidly with glucose indicates that the urinary suppression is due more likely to spasm of the renal capillaries rather than to edema of the kidney. Examination of the capillaries of the nail bed has shown that the circulation improves during glucose administration. In some cases, we have seen the beading disappear. Furthermore, when the serum proteins are high, the osmotic pressure exerted by them in the kidney holds water in the capillaries; but when they are low diuresis is apt to occur. Therefore, in eclampsia after delivery if the capillary spasm could be relieved, a marked diuresis should occur, for the blood pressure is high, the proteins are low and the water content of the blood is increased. A negative water balance after delivery in eclampsia with a urine output of 4 to 5 or even 6 liters is common. Another factor is the increase in P_H which increases the base binding property of the serum proteins and also increases their water binding power.

In eclampsia we find that after glucose injection the chlorides are increased in the urine, and since they are an electrolyte, they will exert a greater osmotic pressure than glucose, thus resulting in a greater diuresis. Their excretion indicates that the kidney is attempting to maintain the osmotic equilibrium of the plasma and since the blood sugar is being constantly increased, this can probably be accomplished more easily by excreting chlorides, which exert a greater

osmotic pressure than glucose. A gram of NaCl will exert slightly more than five times as much osmotic pressure as a gram of glucose.

Cushny states that glucose diuresis resembles that of urea in most points and may be accounted for in the same way by the failure of the epithelium of the tubule to take up the excess of sugar and its inability to absorb water against the osmotic pressure of sugar. He finds that following the injection of intravenous glucose, the concentration of sugar in the urine rises continuously while the chloride falls, especially during the ebb of diuresis. At this stage, therefore, the sugar is falling in the blood and rising in concentration in the urine, while the chloride is not changing in the blood but is falling in the urine. He states that apparently the glucose penetrates into the tissues and displaces the salt. In our studies, both in normal nonpregnant, normal pregnant and in eclamptics, we find that glucose does replace serum chloride. Table VII represents the changes produced in the blood and urine in a normal 87-kilo male by 500 c.c. of 20 per cent glucose solution (100 gm.) injected intravenously over a period of thirty-one minutes. There were no ill effects noted. Δ, the depression of the freezing point of the serum, remained fairly constant, thus indicating a constant osmotic pressure of the serum. Therefore, the increased molecular concentration of the glucose was compensated for by a reduction in the electrolytes. Unfortunately we followed only the serum chlorides but with only these we find that the decrease in osmolar concentration of the chlorides followed closely the increase in glucose. However, one hour after the injection all findings were similar to those before the injection. In the toxemic and especially the eclamptic patient this is not true. Table VIII contains data obtained from a case of nephritis following a salvarsan injection. The patient was given 500 c.c. of a 20 per cent solution of glucose over a period of thirty-three minutes. A more marked reduction of chlorides occurred than in W. J. D. The cell volume returned to normal but the serum proteins remained below their initial reading. Table IX contains data obtained from an eclamptic patient who received 1000 c.c. of a 20 per cent solution of glucose (200 gm.) over a period of thirty minutes. Here again the chlorides showed marked reduction. The cell volume returned to its initial reading; but the proteins remained low. Thus the effect produced on the serum proteins especially but also on the blood as a whole by intravenous injections of glucose solution is similar to delivery, and in the mild case often initiates a cure of the disease; while in the severe it is palliative until delivery or fetal death occurs.

It has been known for a long time that in pregnancy there is a storage of chloride more likely due to the retention of water with a resultant retention of salt than to failure of the kidneys to excrete chloride, although in the pregnant sheep there is a definite retention of NaCl. (Lundin and Scharf.) In eclampsia this storage is markedly increased

even though there is no marked edema and the early convulsions in the majority of cases are, we believe, due to an edema of the brain which thus explains our control of convulsions with the glucose. We have found that the urine from eclamptics on admission, although concentrated as a rule, is relatively low in chlorides but after delivery or the death of the fetus the chloride concentration increases despite the diuresis which occurs. In the normal individual as the urine becomes more dilute the concentration of chloride decreases, but in the toxemics the reverse is true, and we have been able to cause marked excretions of chlorides in the urine by injecting glucose. In Table X we present data from a case of toxemia of pregnancy. The patient was admitted on August 17, 1928, because of headache and edema of the feet. The blood pressure was 215/120 and the urine contained a faint trace of albumin. On the seventeenth, eighteenth, nineteenth, and twentieth the amount of urine and chloride content varied but was in accord while the concentration was inversely proportional to the amount which is normal. Following the injection of 800 c.c. of a 30 per cent solution of glucose not only was the amount of urine and chloride increased but likewise the concentration of NaCl. This phenomenon occurred on each day that glucose was given. On the twenty-third and twenty-sixth no glucose was given and although the volume of urine remained high the chloride excretion was low. This decrease in chloride content after the washing out by glucose is due to retention by the body to replace tissue chloride. Since glucose replaces electrolyte, especially chloride, in the normal individual both in the blood and tissues, it is evident why the eclamptic patient with a tissue chloride retention will have a greater tolerance for glucose since the replacement is apparently based on the relative osmotic pressure exerted by chloride and glucose and not on their respective molecular concentrations. In some diabetic patients, Peters and coworkers find low serum chlorides and infer that the tissues are likewise deficient in chloride. Experimentally it has been demonstrated that there is an inverse relationship between the concentration of glucose and chloride in the blood after the injection of glucose, and it has been suggested that the chlorides possess the property of shifting to other tissues from the blood in order to preserve the optimal osmotic conditions in the blood (Foshay, Herrick).

A study of our cases has proved that the mild cases recover irrespective of the treatment, providing it is of a conservative nature, but in the severe type recovery is markedly favored by early death of the fetus or delivery. Since the blood dilution with its accompanying phenomena occurs after delivery or after death of the fetus, it is considered of prognostic value. Thus, for example, if, after the patient has been in our hands for eight to twelve hours and has been treated

as outlined, we find that the blood is not diluting, that there is no satisfactory diuresis, that coma is either not clearing up or is developing and that the temperature and pulse are increasing, then it is evident that the case is not only a severe one but delivery must be completed within a short period of time without additional shock. If delivery cannot be completed through the natural passage readily, then we prefer abdominal cesarean section under local anesthesia.

Table XI is self-explanatory. Our series is small but it has been carefully culled. A number of cases in whom the occurrence of convulsions was reported were excluded if the laboratory findings and subsequent clinical course were normal. (None of these died.) In the mild type one would expect no maternal mortality. In the severe type there will always be some maternal mortality and a high fetal mortality.

CASE HISTORIES

TABLE II. M. W. 1760

DAY	CELL VOL. PER CENT	SERUM PROTEIN PER CENT	GLUCOSE GM. INTRA "V"	GLUCOSE GM. URINE	URINE C.C.	NaCl GM.	NaCl PER CENT	WEIGHT KILO.
4–10	41.6	6.4						166
11	46	5.68	385					Delivery
12	27	4.43	200 (11 and 12)	22	7200	12.3	0.17	
13				13	2000	13.2	0.66	
14	28	4.92		0	4000	20.4	0.51	
15			90	0	5100	26.5	0.52	
16				0	4300	15.9	0.37	130
17	30	5.7		0	5500	21.4	0.39	
18					4000	26.8	0.67	
19	30.6	5.38			1400	7.1	0.51	
20					2500	7.3	0.27	
21					3900	9.4	0.24	
22					3000	8.4	0.28	
23	32	6.45			3100	6.2	0.205	121
24					2900	7.85	0.27	
25					2700	8.35	0.31	
26					2300	6.45	0.28	
27	36	7.05			2100	5.65	0.27	120
28					2150	5.57	0.26	
29					1500	4.5	0.30	
30					2600	7.28	0.28	
5–5	36	7.23						116

M. W., 1760, primipara, thirty-four years old. At term. On April 6, 1928 patient had two convulsions and on April 10 she had four more. Admitted to hospital on April 10, 1928. She was very obese, in coma, and had a general edema. Blood pressure was 230/140. Urine coagulated on heating. During a period of fifteen hours the patient received 385 gm. of glucose intravenously and voided 1100 c.c. She became conscious. In view of the duration of the disease and the fact that the patient was now in the best condition that could be expected, a cesarean section under local anesthesia was done. A living 5110 gm. baby was delivered. Discharged on May 4, 1928. Note: The decrease of serum proteins before delivery. Marked blood dilution, diuresis, and weight loss (50 kilo in three weeks) after delivery.

TABLE III. E. A. 3380

DAY	CELL VOL. PER CENT	SERUM PROTEIN PER CENT	GLUCOSE GM. INTRA "V"	GLUCOSE GM. URINE	URINE C.C.	Nacl GM.	Nacl PER CENT	WEIGHT KILO.
10–18	45	5.55	440	120	2000	1.8	0.09	165
19	49	5.52	880	154	3350	5.3	0.16	Delivery
20	41	4.15	396	98	3060	5.8	0.19	
21	40	4.26	420	239	3810	7.7	0.20	
22	34	4.85	480	126	3450	6.5	0.19	
23	39.5	4.82	430	155	3250	5.8	0.18	
24				0	1300	0.7	0.05	
25				0	2075	0.5	0.02	
26	30	5.15		0	3250	1.0	0.03	
30	24.5	5.1						
11– 5	35	6.26						

E. A., 3380, primipara, sixteen years old. Forty-one weeks gestation. Normal pregnancy. Admitted on October 18, 1928. Had had headaches and dizziness for past two days. Blood pressure 142/75. Edema of ankles and face. Urine contained a large amount of albumin. Phenolsulphonephthalein test, 70 per cent in two hours with total urine output of 550 c.c. Four hours after admission patient had a convulsion and blood pressure rose to 170/110. During the next fifteen hours she had three more convulsions but despite 42 c.c. of 25 per cent $MgSO_4$ solution given during this period together with 2000 c.c. of 20 per cent and 800 c.c. of 30 per cent glucose solution intravenously, patient gradually became comatose, with temperature rising to 39.8° C. and pulse to 132. Patient was having contractions and the cervix admitted 1 finger, but delivery from below could not be completed under twelve to eighteen hours at a minimum, therefore, a cesarean section under local anesthesia was performed. A living 3450 gm. baby was delivered. Discharged November 9, 1928. Note: The steadily increasing blood concentration despite treatment. Marked dilution and diuresis after operation.

TABLE IV. W. P. 2734

DAY	CELL VOL. PER CENT	SERUM PROTEIN PER CENT	GLUCOSE GM. INTRA "V"	GLUCOSE GM. URINE	URINE C.C.	Nacl GM.	Nacl PER CENT	WEIGHT KILO.
8–12	34	5.13	400	7	500	0.85	0.17	
13	32.6	4.5	350	29	1650	0.93	0.06	
14			200		700			71
15				0	400	0.14	0.035	
16				0	500	0.01	0.002	
17	31.6	4.69		0	1630	0.23	0.014	72
18	55.2	5.60	100	12			0.006	
19	46	4.94	350	0	600	0.04	0.006	Delivery
20	32	4.28		0	5900	2.71	0.046	
21				0	5150	10.3	0.2	
22				0	5300	20.14	0.38	60
23				0	3800	13.4	0.35	
24	32	5.28		0	1600	4.4	0.276	

W. P., 2734, primipara, nineteen years old, thirty-six weeks gestation. Admitted on Aug. 12, 1928 on account of headache, edema of ankles and blood pressure of 180/110. Urine coagulated on heating. Received 1000 c.c. of 20 per cent glucose solution intravenously once or twice daily. Phenolsulphonephthalein test on Aug.

17, 1928 was 25 per cent for two hours. Despite treatment the urine output steadily decreased, blood pressure remained high, and headaches became more frequent. Patient had a Braun bag inserted on August 19 and after a twenty-five hour labor was delivered by perineal forceps of a living 2360 gm. baby. During labor the patient had one convulsion but was not delivered until twelve hours later. On August 31, P. S. P. was 70 per cent for two hours. Discharged on Sept. 1, 1928. Note: The blood dilution on admission which became concentrated at time of convulsion. Oliguria developing while under treatment and almost *complete disappearance of chloride from the urine*, associated with a rapid gain in weight. Marked diuresis postpartum during blood dilution phase, with relatively high concentration of urine chloride.

TABLE V. F. F. 11738

DAY	CELL VOL. PER CENT	SERUM PROTEIN PER CENT	GLUCOSE GM. INTRA "V"	GLUCOSE GM. URINE	URINE C.C.	NaCl GM.	NaCl PER CENT	WEIGHT KILO.
7–18	46.4	6.0	575		600			77.6
19	34	3.82	200	7	900	1.0	0.011	
20	34	3.89	400	1	400	0.2	0.058	Death of fetus
21	34.6			0	2400			
22				0	4000	2.0	0.053	
23				0	6600	7.3	0.110	
24				0	5400	6.4	0.119	
25	36	4.71		0	1300	3.7	0.140	
26				0	1300	2.2	0.168	
8– 3	31.8							
8–17	40	6.35						62.5

F. F., 11738, primipara, seventeen years old, thirty-six weeks gestation. Edema of ankles for past week. Headache and dizziness for past twelve hours. Admitted on July 18, 1927, having already had 2 convulsions. Blood pressure 180/120. Marked edema of feet and legs. Urine coagulated on heating. Patient had 2 more convulsions during first four hours in hospital. No fetal movements were noted by the patient after July 20. On July 21, the P. S. P. was 70 per cent for a two hour total. On July 25 bougies were inserted and after an eighteen hour labor a macerated 2130 gm. baby was delivered. Discharged Aug. 17, 1927. Note: The blood concentration on admission and the marked dilution which occurred twenty-four hours later before death or delivery of the fetus. The protein dropped 36.7 per cent and the cell volume 27 per cent. A marked diuresis together with increasing concentration of urine chlorides occurred after death of the fetus.

CASE HISTORIES OF PATIENTS WHO DIED

A. K., 5365, gravida v, twenty-nine years old, twenty-four weeks gestation. Over a period of two months had had attacks of epigastric pain and vomiting. On Jan. 14, 1924 had similar attack and began to have convulsions. Admitted on Jan. 15, 1924. Deep coma. Temperature 39.8° C. Pulse 144. Respiration 46. Blood pressure 140/?. Urine coagulated on heating. During the twelve hours before death patient received approximately 5000 c.c. of fluid together with stimulants. No urine obtained after initial specimen. Autopsy Diagnosis: Eclampsia. Acute tubular nephritis. This patient was considered moribund on admission because of irregular, rapid, thready pulse, anuria, duration of the disease and the deep coma. The liver was almost completely destroyed by hemorrhage and necrosis.

S. L., 7315, primipara, twenty-six years old, thirty six weeks gestation. Edema of legs for month. Headache, spots before eyes, pain in epigastrium for last four days. Had 2 convulsions before admission on Oct. 16, 1926. She was in deep coma and very edematous. Urine contained large amount of albumin. Blood pressure 180/125. Had one convulsion shortly after admission. Within twenty-four hours following treatment the patient was conscious and fully coordinated. On October 18 patient began to vomit and abdomen became distended. Blood pressure had risen to 210/135. Urine output on eighteenth was 930 c.c., on nineteenth was 2775, on twentieth was 1800 and on the twenty-first was 1050. On the nineteenth approximately 550 c.c. of blood were removed. On the nineteenth, patient

TABLE VI

NUMBER	WEIGHT KILO.	EDEMA	DAY	GLUCOSE GM. INTRA "V"	GLUCOSE GM. URINE	URINE C.C.
M. W.	87.9		22	400	19	720
8392			23	500	28	4900
		Ankles	24	400	28	4040
			25	200	12	2420
			26	200	0	1800
	78.2		27	200	0	2650
F. F.	77.6		18	575		600
11,738	76	Legs	19	200	7	900
	62.5		20	400	1	400
E. B.	70.2		16	400	1	830
440		General	17	750	32	3100
			18	200	57	4500
N. C.	78.9		16	320	23	1400
1332		Ankles	17	100	0	2500
			18	100	0	4000
	67.5		19	200	0	2100
M. W.	166		11–12	585	22	7200
1760	116	General	13		13	2000
			14	200	0	4000
			15	90	0	5100
W. P.	71		12	200	7	500
2734	72.3	Legs	13	350	29	1650
	60		14	200	0	700
			18	200	0	400
			19	150	12	500
L. W.	72		17	290	35	1500
4129	49.5	General	18	180	36	2000
	47		19	240	65	1600
W. B.	69		2	500	9	1775
4640		Ankles	3	200	62	500
	61.8		4		10	1700
F. S.	69.6		6	400	77	2950
3779		Ankles	7	370	120	2850
			8	200		3650
W. W.	65		25	400	58	1310
3437		Ankles	26	400	118	2100
			27	480	91	2400
	58.2		28		68	2600
E. A.	75		18	440	120	2000
3380		Ankles	19	880	154	3350
			20	400	98	3060
			21	420	239	3810
			22	480	126	3450
			23	440	155	3250

became incoordinated and finally unconscious with a temperature of 38.4° C. and pulse of 150. On the twentieth, a Voorhees bag was inserted and the fetus delivered after a twelve hour labor. Death occurred on October 21, apparently of pulmonary embolism. Patient should have been delivered on the seventeenth, when the maximum improvement had occurred.

TABLE VII. W. J. D.

TIME	CELL VOL. PER CENT	SERUM PROTEIN PER CENT	PLASMA Nacl MG.	PLASMA B.S. MG.	Δ	GLUCOSE GM. INTRA "V"	GLUCOSE GM. URINE	URINE C.C.	Nacl GM.	Nacl PER CENT
0	48.5	7.38	586	97	0.544	100 gm.		110	1.06	0.96
15 min.	44	6.13	573	450	0.532					
30 min.	42	5.53	555	550	0.56					
1 hr.							11	358	1.32	0.34
1 hr. 40 min.	48	7.28	590	159	0.546					
2 hr.							4	230	0.49	0.21
3 hr.							0.1	25	0.25	1.0

TABLE VIII. A. H. 2329

TIME	CELL VOL. PER CENT	SERUM PROTEIN PER CENT	PLASMA Nacl MG./100 C.C.	PLASMA B. S. MG./100 C.C.	GLUCOSE INTRA "V" MG./100 C.C.
0	39	6.47	585	92	100 gm.
12 min.	34	5.4	545	565	
33 min.	32.7	5.2	508	690	
1 hr. 35 min.	36.3	6.06	600	195	

TABLE IX. M. B. 4640

TIME	CELL VOL. PER CENT	SERUM PROTEIN PER CENT	PLASMA Nacl MG./100 C.C.	PLASMA B. S. MG./100 C.C.	GLUCOSE INTRA "V" MG./100 C.C.
4–28 A.M.	40	7.47	619	108	200 gm.
15 min.	36	5.75	554	590	
33 min.	34.5	5.1	548	912	
1 hr. 43 min.	39.5	6.4	566		
4 hr. 13 min.	41	6.62	578		
9 hr.	40	6.6	566		
4–3 A.M.	30	5.38	579	82	
4–4 A.M.	27	5.65	531	77	

M. B., 4640, primipara, thirty-nine weeks gestation. Admitted on March 31, 1929. Blood pressure 130/80. On April 2 after patient had been in labor for twenty-four hours with low fluid intake and output, she had a convulsion with blood pressure of 170/115. Delivery was completed nine hours later by perineal forceps. Baby was living and weighed 3165 gm. Discharged April 22, 1929. Classified as mild. Note: Following the glucose injection, the serum protein dropped and remained low although the cell volume returned to its initial reading until after delivery. Marked drop in plasma chlorides during glucose injection.

TABLE X. O. H. 2796

DAY	GLUCOSE GM.		URINE	NaCl	NaCl
	INTRA "V"	URINE	C.C.	PER CENT	GM.
17		0	1240	0.4	5.0
18		0	2200	0.2	4.4
19		0	1850	0.26	4.8
20		0	1700	0.26	4.4
21		0	2900	0.19	5.5
22	225	61	3400	0.27	9.2
23		0	2525	0.07	1.8
24	225	74	3300	0.15	5.0
25	270	64	3250	0.14	4.6
26		0	2300	0.056	1.3
27	270	75	3400	0.16	5.4

TABLE XI. CASES OF ECLAMPSIA, 1923-1929

CASES	NUMBER	POST-PARTUM	SPONTANEOUS ONSET OF LABOR	INDUCTION OF LABOR	CESAREAN SECTION	MATERNAL MORTALITY	BABY	
							LIVING	DEAD
Mild	15	6	8	1	1		15	
Severe	18		7	4	4	3 (2 undelivered)	10	6 misc.
Total	33	6	15	5	5	3	25	6

W. H., 3283, gravida ii, thirty-five years old, twenty-eight weeks gestation. Admitted as a private patient on Oct. 8, 1928 at 8 A.M. because of vomiting and loss of consciousness. Onset was about eight hours before admission. Shortly after entry she had a convulsion. Blood pressure was 195/105 and a slight edema existed. Urine coagulated on heating. Therapy consisted of 500 c.c. of 20 per cent glucose solution intravenously, 1000 c.c. of Ringer's solution subpectorally and 10 c.c. of a 25 per cent solution of $MgSO_4$ at 11 A.M. At 4 P.M. 800 c.c. of urine were obtained by catheter. At 7 P.M. patient was given 250 c.c. of a 20 per cent glucose solution intravenously and 1000 c.c. Ringer's subpectorally. At 9 P.M. 300 c.c. of blood were removed. Stimulants were started at this time. At 10 P.M. 250 c.c. of urine were obtained by catheter, 11 P.M. venesection of 500 c.c. of blood, 11:45 P.M. patient given glucose and 450 c.c. citrated blood. Stimulants continued. Respiration gradually increased until the rate was 40 to 50 per minute. Death occurred at 8 A.M., twenty-four hours after admission. Autopsy Diagnosis: Eclampsia. Focal necrosis of liver. Degeneration of the kidneys. The ease with which a diuresis was established with the small amounts of fluid, the early admission to the hospital after the onset together with the duration during which the patient was treated warrant the belief that more intensive use of hypertonic glucose solution and delivery in the afternoon would probably have resulted in recovery.

SUMMARY

Eclampsia is best treated by certain definite procedures which by their success or failure permit one to note the progress of the case. After delivery or death of the fetus a marked blood dilution takes place, during which period a diuresis occurs. Clinical improvement is closely associated with these phenomena. The eclamptic patient has an increased tolerance for glucose, probably due to the retention of chlorides found in pregnancy. The injection of large amounts of intra-

venous glucose solution will simulate temporarily at least the effect produced by delivery. The prognosis for the patient with a severe type of eclampsia is chiefly favored by delivery or early fetal death.

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THE KIDNEY OF PREGNANCY*

By John C. Hirst, A.B., M.D., F.A.C.S., Philadelphia, Pa.

THE purpose of the paper is to summarize and coordinate our present knowledge of the kidney of pregnancy, and to present certain additional information. The title is used in a broad sense to include the following study:

1. The diagnosis of hydronephrosis, infected hydronephrosis, and pyelitis complicating pregnancy, with a comparison of the relative frequency of appendicitis and gall bladder disease.

2. The relation of hydronephrosis and pyelitis to early and to late gestational toxemia.

3. Differential kidney function tests and pyelograms to discover additional factors in the cause of the common hydronephrosis of pregnancy, with special attention to the possibility of ureteral edema or chronic passive congestion, that might be a contributing cause to late gestational toxemia and eclampsia.

4. An attempt to differentiate renal and hepatic toxemia of pregnancy by the effect of heparmone administration.

Our study therefore contains a review of over seventy leading articles, not only on the above subjects but also on the newer aspects of renal and hepatic function, and the classification of gestational toxemias. The second part contains tables and illustrations from our experience from May 1, 1926, to May 1, 1929, with the behavior of the kid-

*Read by invitation.

ney of pregnancy. For ten years I have had charge of the cystoscopic work in the Department of Obstetrics of the Hospital of the University of Pennsylvania, through the courtesy of the Professor of Obstetrics, first, Dr. Barton C. Hirst, later, Dr. Edmund B. Piper. This arrangement of having one member of the regular Obstetric Staff responsible for the usual urologic complications of pregnancy and the puerperium is an eminently satisfactory one, conducive to proper interest in and to accurate diagnosis of diseases of the maternal urinary tract, without which plan such records as herein given would be impossible.

A summary of the literature as mentioned will not review the pathologic histology of the renal and hepatic parenchyma in the toxemias, including eclampsia, except to mention the description of Schwarz[1] and of Dieckmann,[2] but rather the function and infection of the upper urinary tract, and hepatic function.

In Europe, the urea kidney function tests[3-8] including Ambard's constant, appear to be favored, on the grounds of better estimation of renal reserve, but such tests are technically difficult, and in cystoscopic differential studies they require occluding catheters. Therefore the dye tests, notably indigocarmine, are favored in this country. None of these, nor any urinary findings[9] of the present day alone, will designate a clear-cut type of late gestational toxemia, although there is hope that identification of liver protein in the blood or urine of sensitized rabbits may eventually prove the diagnosis of hepatic toxemia, if there be such an entity.

Neither do routine blood chemistry tests[10] assist to any degree in differentiating renal from hepatic insufficiency in pregnancy. In the University Maternity Hospital during the period of three years from May 1, 1926, prenatal patients with toxemia symptoms or blood pressure over 150 systolic, as well as other toxemic patients, have had careful check of blood urea nitrogen, uric acid, creatinin, blood sugar, CO_2 and Van den Bergh tests, yielding no curve that could be plotted for diagnostic or prognostic significance, except in extreme cases. We recognize, however, a low CO_2-combining power of the blood as a menace requiring alkalinization (Wilson), and appreciate the value of morphine and luminal, glucose, magnesium sulphate, vapor baths, etc., for nearly all types of eclampsia.

The nearest approach to division of the late toxemias may be made by utilization of simple laboratory tests and clinical manifestations,[11] especially blood pressure,[12] eyegrounds, urinary specific gravity, edema, progress of symptoms, and recovery up to six to twelve weeks postpartum. The simple differentiation that we have been teaching students for several years, amplified by Mussey and Keith,[13] is briefly as follows:

A. Acute late gestational toxemia characterized by rapid onset late in pregnancy, with good dye elimination, high urinary specific gravity, and complete recovery within three months of delivery.

B. Chronic late gestational toxemia featured by gradual onset, earlier in pregnancy, frequently as an exacerbation of prior hypertension, often seen in multip-

arae; poor dye elimination, marked eyeground changes, low urinary specific gravity, and incomplete recovery in three months.

Definitions of gestational toxemia, such as preeclamptic, mild, severe, etc., are confusing and have been discarded in our tables in favor of the classification just mentioned. We have not attempted to divide our patients into hepatic toxemias,[11-20] on the basis of liver function tests. Some years ago several of our cases of generalized pruritus complicating pregnancy showed abnormal retention of phenoltetrachlorphthalein,[21] but a small series of so-called hepatic type toxemias failed to demonstrate constant retention of this dye, so that we are unable to depend upon the test in this connection, in spite of the well-known tendency of pregnancy toward hypercholesterolemia, gall bladder disease, and hepatic degeneration.

Fig. 1.—Infected hydronephrosis (35 c.c.) and ureteral edema associated with mild toxemia of late pregnancy. Absence of obstruction and lateral deviation of ureter permitted prompt relief by raising foot of bed. Proof of circulatory cause of impaired ureteral drainage.

Finally in regard to ureteropelvic dilatation and infection, it was inevitable that proof in vivo of extreme frequency in puerperal women, would follow postmortem evidence,[22] such proof having been estab-

lished in numerous articles.[23-28] Close association with late toxemia has also been shown, and lately etiologic factors in the production of the above conditions, which Kretschmer and Heaney[29] were among the first to visualize by pyelography. Most followers attempted to explain ureteropelvic distortion by actual pressure of the gravid uterus,[30-40] increased intra-abdominal tension, stricture,[41] infection,[42-45] and other causes,[47-49] but Hofbauer[50] by a study of morbid anatomy demonstrated the most important factors to consist of hyperplastic and hypertrophic changes in

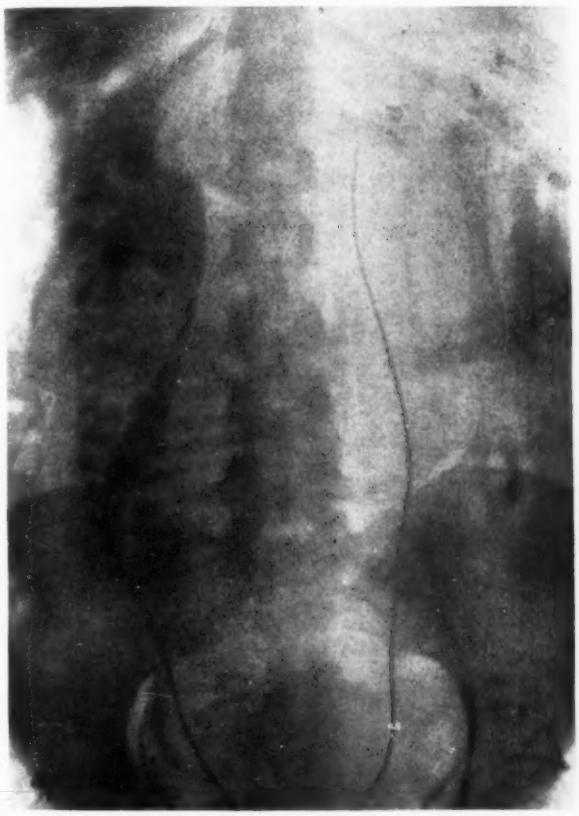

Fig. 2.—The kidney of pregnancy. Lateral deviation of ureter with low grade infection of moderate hydronephrosis (22 c.c.) and typical hydroureter complicating late pregnancy.

the pelvic portion of the ureter including musculature, connective tissue, and sheath, producing a narrow lumen at this point. The latter author also stressed the action of increased bile acid in the mother's blood in reducing uterine, intestinal, and ureteral muscular contraction. Hofbauer's discovery may not quite agree with the very recent report of Frater and Braasch[51] from the ureteral study of 93 autopsies, nearly half of which were women, some pregnant, and some having borne children, in which they found only four abnormal ureteral narrowings, of which two were noninflammatory strictures, one congenital narrowing,

and one extraureteral growth. Atonic dilatation without stricture due to infection was also demonstrated.

Duncan and Seng[52] have contributed invaluable information by proving that many apparently normal pregnancies show latent ureteral infection usually with coliform organisms, atonic dilatation (hypertrophy), and delayed emptying of the ureter, all of which can readily predispose to a toxemic state. The work of Traut,[53] of Morrison[54] on the routes of absorption in hydronephrosis by experimentation with dyes in totally obstructed ureters, and Ferrer's[55] report of obstruction to venous circulation in the kidney caused by distention of the pelvis and

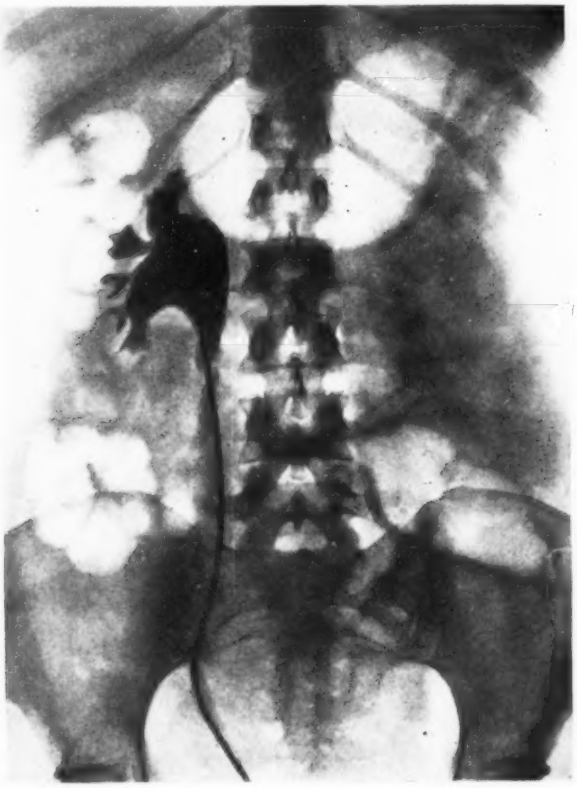

Fig. 3.—Persistence of hydronephrosis, and ureteral kink in same patient thirteen days after delivery. Same result with sterile urine four weeks later.

calices, also bear on the subject of our paper, the first two denoting a guide to possible damage by careless pyelography. These studies support one conclusion from our own observations that late gestational toxemia is for the most part primarily of renal origin, and would explain the report of FitzHugh[56] on the urohepatic syndrome or interrelation of renal and hepatic pathology.

The infrequency of appendicitis, once in 525 pregnancies, suggests a connection between chronic appendicitis and sterility. On the other hand, the remarkable frequency of pyelitis or infected hydronephrosis,

once in 15 pregnancies, contrasts with the report of another Philadelphia Maternity Hospital for one year, giving only 8 or 10 cases of pyelitis in about 1000 pregnancies, the difference being due to method of diagnosis.

TABLE I. FROM THE DEPARTMENT OF OBSTETRICS, HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

Total pregnancy admissions from 5/1/26 to 5/1/29	2101
Pyelitis and infected hydronephrosis	140
Simple hydronephrosis (severe)	23
Gall bladder disease	12
Appendicitis	4
Early gestational toxemia	44
Late gestational toxemia and eclampsia	232

TABLE II. PYELITIS AND INFECTED HYDRONEPHROSIS (POSITIVE CULTURE, PUS, OR FEBRILE WITH SYMPTOMS)

Total number				140
Primiparae	right 39	left 7	bilateral 24	
Multiparae	" 30	" 12	" 28	
Infecting organisms (total cases with positive culture)				26
Coliform				19
Other organisms				7
Onset during pregnancy				116
History of prior urologic disease				24
Medical treatment				82
a. Relapse				4
b. Persisted at follow-up				8
Cystoscopic treatment				58
a. Relapse				2
b. Persisted at follow-up				4
Total cases of:				
Early gestational toxemia				44
Accompanied by pyelitis (active)				3
Vomiting relieved by cystoscopy				1
Late gestational toxemia and eclampsia				232
Accompanied by pyelitis (active)				16
(See tables IV, V, VI.)				

Noticeable is the comparatively small number of positive cultures from pyelitis (26 out of 58 cystoscopies). Our technic may account for this. This is carried out as follows:

All patients are examined under similar conditions as far as possible, that is, at about the same time of the clinic day, without morphine, and after two glasses of water. No. 7 opaque catheters frequently renewed, boiled after use in infected cases, and always injected with and immersed in 4 per cent formalin solution are used, being flushed with sterile water just before introduction. All other apparatus is scrubbed; tables, etc., are prepared exactly as for a major operation, in a special cystoscopic room. Catheter specimens are examined by the William Pepper laboratory. Five c.c. of 0.4 per cent indigocarmine is injected intravenously before ureteropelvic distention is tested which is done after appearance of the dye. Twenty to 30 c.c. (or more) is injected in as many seconds, while the patient is questioned for pain and as the ureteral orifice is watched for blue tinted leakage. The amount of recovery during the time of injection is noted, and checked by many pyelograms, which in virtually all cases have confirmed the first injection.

Whereas early gestational toxemia was complicated in three cases by febrile pyelitis, silent infection of the kidney of pregnancy was present in several more, both primiparae and multiparae, suggesting unrecognized pyelitis in childhood on the part of the former, and persistent kidney of pregnancy of the latter.

Table III, showing an average ureteropelvic content of 15 to 18 c.c., means the minimum average before any leakage, with no pain on injection. In these cases, as in many of the infected hydronephroses, injection of the ureters could usually be done much more rapidly than with normal ureters, often to a surprising maximum of 30 to 50 c.c., denoting atonic dilatation. Several of the more pronounced unilateral hydronephroses showed a definite difference in the urinary specific gravity of the right and left kidneys.

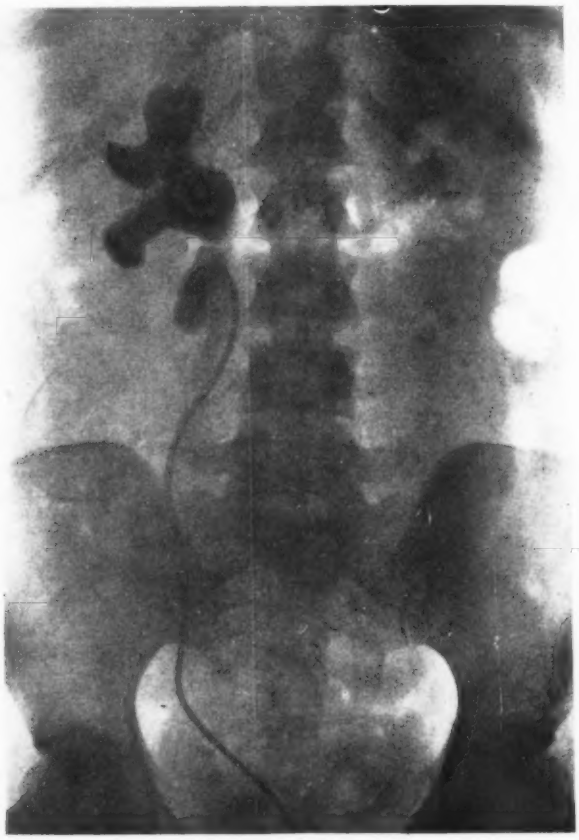

Fig. 4.—Infected hydronephrosis in primipara associated with hyperemesis gravidarum, with history of prior pyelitis. Each condition improved by ureteral lavage and drainage.

Of the 44 early toxemic patients 7 primiparae less than eight weeks pregnant had cystoscopic examinations, only 2 of these showing any evidence of ureteropelvic dilatation.

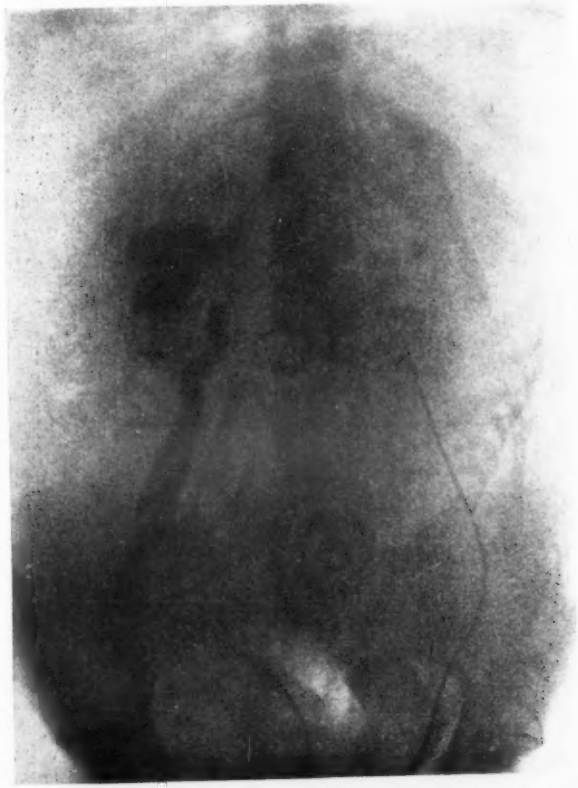

Fig. 5.—Advanced infected hydronephrosis (over 35 c.c.) of pregnancy, probably from pyelitis in childhood. Note extreme lateral deviation and lengthening of ureters.

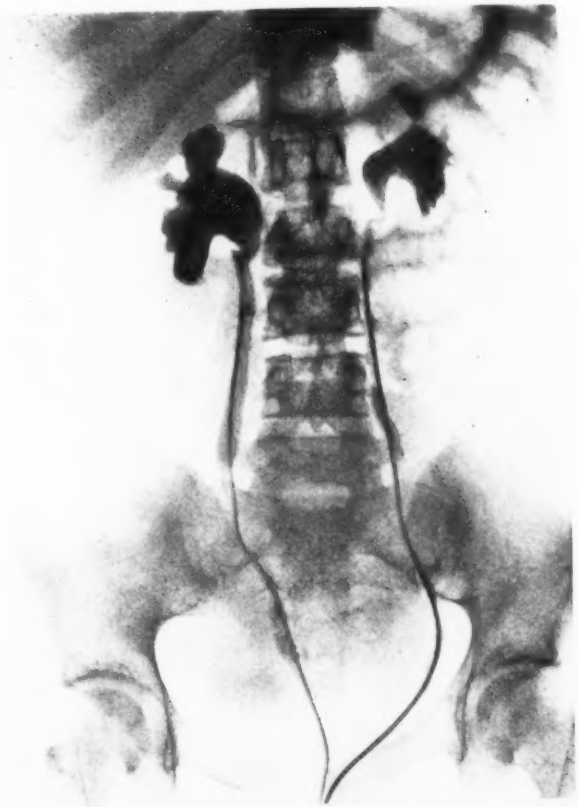

Fig. 6.—Moderate persistence of hydronephrosis in same patient, with ureteral kinking thirteen days after delivery.

Whenever the term severe hydronephrosis appears in this report, it denotes either marked ureteropelvic dilatation proved by cystoscopy and greater than the usual amount in pregnancy, or presumably the same condition designated by objective and subjective symptoms with negative bladder pus and culture.

The rather high figure of 151 in Group A, late gestational toxemias, may be accounted for by the mild degree of many cases which were admitted with moderate hypertension as the main symptom. Although the indigo carmine differential dye tests were fair in the cystoscoped Group B cases, other symptoms warranted such cases to be placed in this group along with many showing reduced phenolsulphonephthalein output. Emphasis on ureteral edema is made to bring up the connection between vasodilatation or circulatory stasis about the distal ureter with late gestational toxemia. Several instances encountered either in association with a very low fetal head, especially in early labor, marked varicosities of vulva, hypertrophic cervicitis, or subinvoluted retroversio uteri, suggest this form of impaired ureteral drainage as a possible cause of certain cases of toxemia.

TABLE III. SIMPLE HYDRONEPHROSIS (NEGATIVE CULTURE, NO CLUMPING OF W.B.C., AFEBRIL)

Total, severe				23
Proved by cystoscopy				14
Primiparae	right 1	left 0	bilateral 3	
Multiparae	" 7	" 0	" 3	
Average pelvicureteral content (over)				15-18 c.c.
History of prior urologic disease				3
Stone				2
Stricture(?) (Not present at this time)				1
Onset during pregnancy				21
Cystoscopic treatment				14
Relapse				2
Persisted at follow-up				0
Early gestational toxemia				44
Accompanied by hydronephrosis (severe)				1
Vomiting relieved by cystoscopy				1
Late gestational toxemia and eclampsia				232
Accompanied by hydronephrosis (severe) (See tables IV, V, VI.)				17

The reason for the favorable dye tests in the 5 cystoscoped eclamptics can be explained by convalescence. One-third of the 23 eclamptics showed marked hydronephrosis or pyelitis. From 1915 to 1920 approximately 100 eclamptics were admitted to the University Maternity ward from various sources, of whom 14 died. From May 1, 1926, to May 1, 1929, 23 eclamptic patients were admitted, only 2 from our own prenatal division, of whom 3 died.

UROLOGIC SUMMARY

Certain significant facts are brought out by a summary of the 97 obstetric patients subjected to urologic diagnosis by cystoscopy and pyelography:

1. Ureteral obstruction appeared only four times, in the form of calculus twice, congenital narrowing of the orifice and stricture. This absence of frequent obstruction presupposes some additional factor responsible for impaired drainage not accounted for by atonic ureteral dilatation or latent infection so common in pregnancy. This impairment we believe is circulatory in the form of intermittent

TABLE IV. LATE GESTATIONAL TOXEMIA

A. Acute: late pregnancy, rapid onset, high urinary specific gravity, good dye test, complete recovery in 6-12 weeks.	
Total cases	151
Accompanied by:	
Hydronephrosis (severe)	4
Pyelitis (active)	5
Cystoscoped:	
Hydronephrosis	4
Primiparae right 2 left 0 bilateral 0	
Multiparae " 1 " 0 " 1	
Indigocarmine diff. (average)	
Right 8 min, left 7 min.	
Evidence of ureteral edema corresponding with the hydronephrosis	3
Pyelitis	3
Primiparae right 0 left 0 bilateral 2	
Multiparae " 0 " 0 " 1	
Indigocarmine diff. (average)	
Right 5 min., left 7 min.	
Evidence of ureteral edema corresponding with the pyelitis	0

TABLE V. LATE GESTATIONAL TOXEMIA

B. Chronic: starting earlier in pregnancy, slow progress, older multiparae often, or prior hypertension, low urinary specific gravity, poor dye test, eyeground changes, poor recovery.	
Total cases	58
Accompanied by:	
Hydronephrosis (severe)	8
Pyelitis (active)	7
Cystoscoped:	
Hydronephrosis	7
Primiparae right 1 left 0 bilateral 1	
Multiparae " 3 " 1 " 1	
Indigocarmine diff. (average)	
Right 3 min., left 8 min.	
Evidence of ureteral edema corresponding with hydronephrosis	3
Pyelitis	5
Primiparae right 0 left 1 bilateral 1	
Multiparae " 0 " 0 " 3	
Indigocarmine diff. (average)	
Right 7 min., left 10 min.	
Evidence of ureteral edema corresponding with pyelitis	3

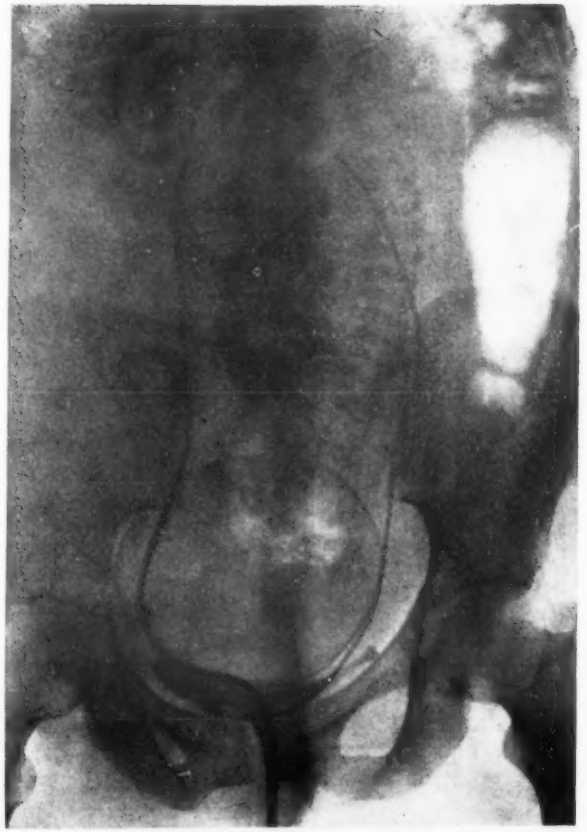

Fig. 7.—Bilateral infected ureteropelvic dilatation due to calculus six years before, associated with a seven months' pregnancy, without toxemia. Note course of right catheter.
Normal appendix removed before admission.

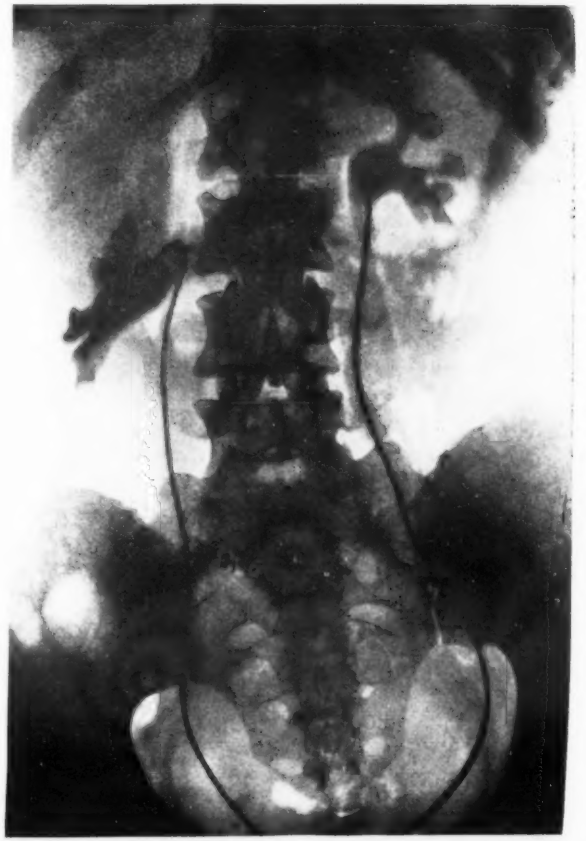

Fig. 8.—Bilateral nephroptosis before pregnancy. Reclining.

six years before, associated with a seven months' pregnancy, without toxemia. Note course of right catheter.
Normal appendix removed before admission.

Fig. 8.—Bilateral nephroptosis before pregnancy. Reclining.

Fig. 9.—Sitting posture. Same patient as shown in Fig. 8.

Fig. 10.—Same patient as Fig. 8 in late pregnancy. Moderate hydronephrosis, considerable pain, relieved by posture.

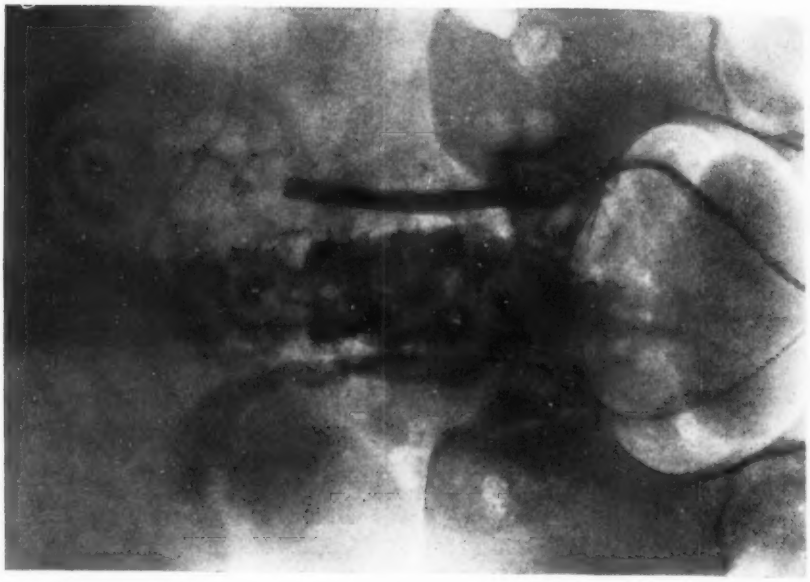

Fig. 12.

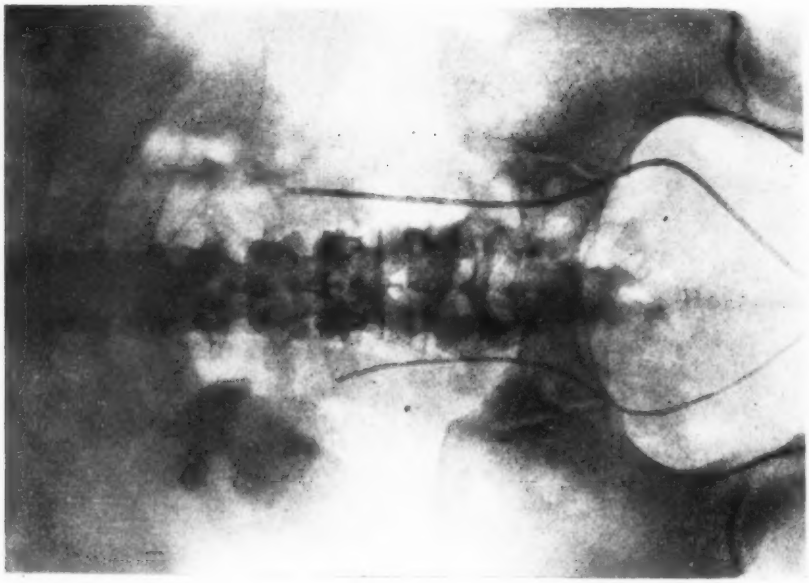

Fig. 11.

Figs. 11 and 12.—Large calculus in right pelvis, and stricture of left ureter, with bilateral infection, six weeks after delivery. The effect of infected hydronephrosis beginning in pregnancy, and the cause of severe late gestational toxemia.

vasodilatation or chronic passive congestion of and around the distal ureter, evidenced by edema of the orifice in the form of irregularity of shape and puffing.

2. Jaundice did not appear in any case, but one instance of subacute exacerbation of a chronic cholecystitis followed ureteral catheterization. Therefore it appears that even if the renohepatic interrelation be of importance in infection and toxemia, it plays no great part in careful cystoscopy of the obstetric patient.

3. Other harmful results of urologic investigation included two troublesome increases in severity of chronic pyelitis, and one precipitation of labor at term.

TABLE VI. LATE GESTATIONAL TOXEMIA

C. Eclamptic Type (of Groups A and B) total	23
Group A. Acute	17
Accompanied by:	
Hydronephrosis (severe)	3
Pyelitis (active)	3
Cystoscoped:	
Hydronephrosis	2
Primipara right 0 left 1 bilateral 0	
Multipara " 0 " 0 " 1	
Indigocarmine diff. (average)	
Right 4½ min., left 3 min.	
Evidence of ureteral edema corresponding with the hydronephrosis	2
Pyelitis	2
Primipara right 0 left 1 bilateral 0	
Multipara " 0 " 0 " 1	
Indigocarmine diff. (average)	
Right 9½ min., left 8½ min.	
Evidence of ureteral edema corresponding with the pyelitis	2
Group B. Chronic	6
Accompanied by:	
Hydronephrosis (severe)	2
Pyelitis (active)	0
Cystoscoped:	
Hydronephrosis	1
Primipara none	
Multipara right 1 left 0 bilateral 0	
Indigocarmine diff.	
Right 20 min., left 4 min.	
Evidence of ureteral edema corresponding with the hydronephrosis	1

Heparmone table (Table VIII) speaks for itself, but fails to mention the sudden headache so commonly produced by intravenous injection, which should be by slow drip or discarded in favor of intramuscular administration. No dangerous reactions occurred, but also no marked symptomatic improvement was maintained after injections were stopped, with one brilliant exception where heparmone alone cured a very ill woman.

The 27 cases were reported on toxemia record forms provided by the Committee on Toxemia of the Philadelphia Obstetrical Society. Dr. Woodward of the Eli Lilly Research Department very kindly furnished the heparmone for experimental use, offering explanation of the product and suggestions for its use, for which we extend grateful thanks.

Figs. 11 and 12.—Large calculus in right pelvis, and stricture of left ureter, with bilateral infection, six weeks after delivery. The effect of infected hydronephrosis beginning in pregnancy, and the cause of severe late gestational toxemia.

TABLE VII. EFFECT OF HEPARMONE ON LATE GESTATIONAL TOXEMIA (HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA)

Total cases Group A			2
Average	*Before*	*After*	
Blood Pressure	160/80-190/110	140/80-180/110	
Blood Urea Nitrogen	14 mg.	13.0 mg.	
Blood Uric Acid	5 mg.	3.5 mg.	
CO_2 vol. per cent			
Blood Sugar	81 mg.		
Van den Bergh	normal	normal	
Average quantity injected per case			80 c.c.
Number cases of eclampsia after heparmone			0
Total cases Group B			6
Average	*Before*	*After*	
Blood Pressure	148/94-222/118	138/88-220/110	
Blood Urea Nitrogen	12.0 mg.	12.0 mg.	
Blood Uric Acid	4.0 mg.	3.6 mg.	
CO_2 vol. per cent	56.0	51.0	
Blood Sugar	76.0 mg.	94.0 mg.	
Van den Bergh	normal	normal	
Average quantity injected per case			280 c.c.
Number cases of eclampsia after heparmone			1
Total cases of eclampsia in 3 years			23
Total cases of eclampsia in which heparmone was used			9
Results:			
Cases requiring additional treatment			8
Cases requiring operative interference			5
Deaths			0

TABLE VIII. USE OF HEPARMONE IN LATE GESTATIONAL TOXEMIA

Type A. Toxemia	Total	9
Average maximum blood pressure	188 mm.	
Average maximum reduction under heparmone	43 mm.	
Urinary improvement		3
Symptomatic improvement		6
Result:		
Labor induced		3
Baby died		1
Terminated in eclampsia		0
Type B.	Total	9
Average maximum blood pressure	200.0 mm.	
Average maximum reduction under heparmone	31.1 mm.	
Urinary improvement		1
Symptomatic improvement		2
Result:		
Labor induced		6
Baby died		3
Terminated in eclampsia		0
Eclampsia	Total	9
Average maximum blood pressure	173 mm.	
Average maximum reduction under heparmone	44 mm.	
Relief of convulsions		2
Operative interference		4
Result:		
Mother died (insufficient heparmone—1)		2
Baby died		3

TABLE IX. CYSTOSCOPIC STUDY OF "NORMAL" PREGNANCIES (LATE PREGNANCY)

Total				15
Hydronephrosis (moderate)				11
Multiparae	right 1	left 0	bilateral 1	
Primiparae	" 7	" 0	" 2	
Cultures:				
Reported "no growth"				5
B. Coli				3
Hem. Strep. pyogenes				1
Hem. Staph. albus				2
Diff. Indigocarmine (average) Right, 8 min., left 8 min.				
Evidence of ureteral edema				6

TABLE X. CYSTOSCOPIC DIAGNOSIS OF 119 CONSECUTIVE GYNECOLOGICAL PATIENTS FROM MAY 1, 1926, TO MAY 1, 1929

1. *Cystitis*				16
	Acute	4		
	Chronic	12		
2. *Pyelitis*				39
Right	Acute	0		
	Chronic—coliform	15		
	Other	10	(Including pus but no growth.)	
Left	Acute	0		
	Chronic—coliform	4		
	Other	1		
Bilateral	Acute	4		
	Chronic—coliform	4		
	Other	1		
3. *Hydronephrosis*				14
Right		11		
Left		2		
Bilateral		1		
4. *Pyonephrosis*				
Right				1
5. *Ureteral obstruction*				14
Kink		1		
Calculus		3		
Stricture				
Right (Postoperative—3)		6		
Left		2		
Congenital narrowing—left		2		
6. *Normal cystoscopy*				19
7. *Questionable diagnosis*				8
8. *Tuberculosis*				2
9. *Nephroptosis*				
Right				1
Bilateral				1
10. *Urethral stricture*				1
11. *Vesicovaginal fistula*				1
12. *Horseshoe kidney*				1
13. *Urethritis*				1
				119

(One-half of the total showed pyelitis or hydronephrosis without obstruction; of this number (53) 39 had borne children or miscarried, of whom 23 noticed the onset during pregnancy or shortly after.)

These trials were endorsed by our personal observation of the work of Miller and Martinez, whom we found earnestly endeavoring to follow their use of heparmone with individual attention and careful thought.

The opinions accompanying the above heparmone reports may be briefly expressed as follows:

Heparmone will reduce blood pressure, but for the most part only during treatment.

It must be supplemented with other measures.

It produced headache in many instances; instituted convulsions in one case; caused very sharp reaction in one case.

Very favorable improvement maintained after discontinuance of injections was noted in four women.

After the work of Duncan and Seng, Kretschmer, and others, we hesitate to include the "normal" table, which shows usual conditions. Of much interest, however, is the list of gynecologic urologic conditions.

Finally, from an attempt to combine the reference articles, and from the foregoing tables, certain conclusions appear sound:

1. Cystoscopic urologic diagnosis is an important part of an obstetric service, and when carefully performed carries no undue risk.

2. Vasodilatation and circulatory stasis of the distal ureter may directly or indirectly be concerned with late gestational toxemia.

3. Early and late toxemia are essentially different; the latter is primarily renal in origin.

4. Heparmone appears to bear insufficient specific action to separate a hepatic type from the late forms of pregnancy toxemias.

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When an ovarian cyst is discovered during the first trimester the accepted form of treatment is oophorectomy. However, Brouha feels that where the cyst is not discovered until the latter months, this procedure may result in either premature labor or rupture of the abdominal wall at term. In those cases where the cyst is in front of the presenting part an attempt should be made to displace it into the abdominal cavity by vaginal manipulation in either the knee-chest or Trendelenburg position. When such procedure fails, the patient should be allowed to labor until delivery from below could be accomplished if this cyst would not be interfering. At this time the abdomen is opened, the cyst removed and the pedicle ligated. The patient is then placed in the lithotomy position and delivered by either forceps or version. Following delivery the pedicle is reinspected for possible hemorrhage and the abdomen closed. Brouha advocates this procedure because he feels that closure is made easier after reduction in size of the abdomen and because occasionally the ligature on the pedicle may slip during delivery. Delivery from below is preferable to cesarean because the uterine wall is not subjected to surgical damage.

Theodore W. Adams.

THE SIGNIFICANCE OF LOW ARTERIAL PRESSURE IN PREGNANCY

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THE development of the sphygmomanometer gave such a marked stimulus to the study of the physics of the circulation that the use of this instrument has resulted in a magnitude of clinical observations on the cardiovascular mechanism. The application of blood pressure readings to the practice of obstetrics has become universal; particularly have we come to recognize the value of a rising blood pressure as a sign of impending toxemia. In recent years excellent studies have been made upon the course and effect of pregnancy in women with constantly raised blood pressures, the so-called essential hypertension.

In a notable manner low arterial pressure, hypopiesis, has received, in comparison with hypertension, scant attention by clinicians except in the past few years.[1] To my knowledge no discussion of this disturbance of the cardiovascular mechanism as regards pregnancy and labor has been offered, so that I have felt that a brief review of the subject, and an analysis of the histories of fifty women who presented marked hypotension, in one or more pregnancies, with a view to determine whether or not hypotension has any degree of significance as regards the course of pregnancy and labor, might be of considerable interest.

It would be difficult to define hypotension without some statement as to what constitutes normal pressure. Perhaps Faught's rule[2] is as accurate as any offered: "Begin at 120 mm. systolic for an adult male of twenty years and add one point for each two succeeding years. Women have a slightly lower pressure than men." Barach,[3] in discussing hypotension, states that for the sake of uniformity with others, he has adopted the level of 110 mm. of mercury, or less, as indicating arterial hypotension. Osborne[4] says that a systolic pressure of 110 mm. or lower in an adult should be considered hypotension, and even goes so far as to state that anything below 105 mm. calls for treatment, while a systolic pressure of 100 mm. or lower in an adult calls for rest from active duties. Norris[5] says when the pressure goes below 105 mm. few can be on their feet regularly.

In order to accentuate whatever significance low arterial pressure may have in pregnancy I have chosen for review in this paper only those women whose systolic pressures did not rise above 100 mm. during their pregnancies. This figure is considered by Janeway[6] as more truly indicating hypotension.

Cases presenting low arterial pressure are divided clinically into three groups without much difficulty. With acute hypotension we are all familiar. This includes the acute traumatic type, the case of surgical shock, the fall in pressure following prolonged anesthesia, the rapid fall in allergic reactions, and the acute drop often seen at the onset of epidemic influenza. In this group also belong those cases of temporary low blood pressures of the acute infections, influenza, typhoid fever, diphtheria, and pneumonia, and of the early weeks of pregnancy when even moderate hyperemesis gravidarum is present. A chronic low arterial pressure, the second group, is well recognized as a fairly constant finding in tuberculosis, the anemias, myocardial degenerations from such various causes as postinfluenzal weakness, focal infections, and various intestinal disorders including splanchnoptosis. Essential hypotension, the third group, is a condition of persistent low systolic pressure having no obvious exciting cause. For this condition we find many synonyms, the number and terminology of which may be indicative of the failure to properly explain its etiology: neurocardiovascular asthenia, hypoadrenia, hyposphyxic syndrome (Martinet), X-disease (MacKenzie), and constitutional hypotension (Riesman).

The frequency of the last group in general physical examinations, martial and civil, runs about 3½ per cent.[3] Larimore[7] feels that about 19 per cent of women have hypotension, and according to the physical type of the individual, using Mills's[8] classification of hypersthenic, sthenic, hyposthenic, and asthenic, considers that 64 per cent of the latter two classes have hypotension.

The production of normal blood pressure is dependent upon several factors: cardiac tone, the condition of the vessel walls, the peripheral resistance to the blood stream, and the state of the blood itself, volume and viscosity. Friedlander,[9] who has made an exhaustive study of the subject, considers peripheral resistance the most important single factor in the maintenance of normal pressure and the production of hypotension. The state of tonic contraction in which the arterioles and capillaries are normally held is due to impulses derived from vasomotor centers, subject to the rise and fall of these impulses as influenced by various stimuli. Capillaries possess a power of dilatation and contraction independently of the arterioles, and normally they maintain a state of vasomotor tone subject to both chemical and nervous stimuli. The potentially large reservoirs of the capillary bed may form an important factor in the low blood pressure of shock.

Mufson[10] has shown that in cardiovascular hypertensive toxemia the state of the capillary pressure is of prognostic value. A study of this phase of the vascular phenomena in pregnancy which I am making, especially in regard to hypotension, is of too recent beginning to offer any figures or deductions.

According to Friedlander the following theories have been offered to explain the low systolic pressure of essential hypotension: adrenal insufficiency (Lawrence); focal infection (Hoxie); respiratory deficit and decreased oxygenation (Barach); a constitutional inferior state (Levinson); elongation of the ascending aorta with narrowing of its semicircle (Fossier); a splanchnic pooling of the blood (Mosenthal), (Greaves); while Friedlander leans toward capillary stasis due to chronic poisoning from absorption of histamine or histamine-like bodies. Eyster[11] considers hypotension to be due to the dissemination of depressor substances which cause a dilatation of the peripheral vessels and a lowered capillary pressure, though the venous pressure remains the same.

Hypothyroidism and the clinically similar endocrine disturbances cause hypotension according to Barach from a decreased oxygenation consequent upon a lowered basal metabolism. Wright[12] points out that removal of almost the whole of the suprarenal gland has no effect upon the blood pressure of experimental animals. He dismisses the theory of hypoadrenia as a cause of low tension. Moody, Van Nuys and Chamberlain[13] found that 87 per cent of healthy athletic women students at the University of California had the greater curvature of the stomach below the interiliac crest. This finding, when one remembers that splanchnoptosis is given as a cause, shows that no sweeping conclusions should be drawn between constitution and body function. According to insurance companies there has been a very perceptible decrease in systolic pressure and a still more decided decrease in diastolic pressure within the past eight years, which may be partly accounted for by the increase in influenza.

The essential physical characteristics of a typical hypotensive adult picture a constitutionally underdeveloped inferior type; undersized, slender bodies, of a nonathletic build, with narrow nostrils and long necks they present drooping shoulders over a long narrow chest. They are shallow breathers with chest capacity smaller than normal, the costal angle is acute and the ribs consequently slant downward. The diaphragm is pushed downward and flattened, and the epigastrium is sunken above a protuberant hanging abdomen. Often the lumbar spine is straight, or even convex, rather than with a concave curvature.

Their chief complaints are physical exhaustion, lack of endurance and headaches. Such individuals become exhausted physically and mentally very quickly. Graham-Stewart[14] explains their capability of very considerable physical effort as being due to the overtone of the nervous as compared with the vascular system. Memory is often impaired. They complain of vertigo, fainting spells, and persistent headaches. From the circulatory system such symptoms as cold hands and feet or moist, clammy, numb extremities and cyanosis are complained of. While the skin and conjunctiva may present an anemic appearance often the hemoglobin and erythrocyte figures are normal. Many

of these symptoms are probably due to the deficient physical structure or to such associated conditions as splanchnoptosis, and not to the low pressure. Such marked symptoms as those pictured above are seldom seen with levels above 110 mm., but when they fall below this mark they will nearly always be followed by some subjective symptoms.

The prognosis as to life in cases of persistent low pressure is better than in cases where the pressure is normal or above. Fisher[15] of the North Western Life Insurance Company has stated that the death rate in the low pressure series was only 35 per cent of the expected mortality. As a rule these individuals do not lead as strenuous lives as those with higher pressures, and this inactivity may tend to longevity. There is a widely accepted impression that an individual with a decidedly lowered blood pressure is not a good surgical risk, based upon the idea that there is too narrow a margin between safety and shock. Frazer[16] urges that operation on a patient showing persistent low blood pressure should be delayed, if possible, until means have been taken to raise the blood pressure. In his requisites for an elective gynecologic section Polak[17] calls for a blood pressure between 110 and 150 mm. and states that blood pressure has a signal significance in the prognosis of operative patients. Graham-Stewart says that patients with hypotension are not bad operative risks, and that there is no great possibility of shock, possibly because the cardiovascular system is incapable of response.

CLINICAL DATA

Age and Parity.—In analyzing the histories of the 50 women who presented marked low arterial pressure during one or more pregnancies I found that their ages were mostly within the third decade. The 32 primiparous women had been married from three to ten years before pregnancy ensued. Nineteen of them stated that no contraceptives had been used, and in 5 of them various operative measures had been used to relieve sterility. It is possible that the same etiologic factor of the delayed pregnancies in these women may also be a cause in other sterile women who frequently present hypotension. Twenty-one children and 6 miscarriages had occurred among the multiparous women; for the social class of patient observed I feel this a larger than normal proportion of miscarriages, one premature infant died and there were two unexplained stillbirths before term. Fifteen of the 18 children had been bottle-fed from birth.

Medical History.—An effort was made by careful questioning to determine in the previous medical history some cause for the low blood pressure. There were 8 patients with a fairly definite history of ptosis of the stomach, including that of treatment in 3, and 1 of ptosis of the kidney. Influenza had attacked 10 of the patients during the epidemic of 1918, others gave a history of mild influenza in later years. Four

had been treated for cardiac disease, while 2 gave a history of rheumatic fever and 3 of diphtheria, both of which infections, as well as the influenza, may have left a weakened cardiac muscle. Three women gave a history of tuberculosis, 1 of the lung, 1 of the hip joint, and 1 of the glands of the neck. There were 2 others whose diseases of the bones, periostitis and curvature of the spine, pointed to tuberculosis. The menstrual histories showed a delay in onset until fifteen years in 12, and until seventeen years or later in 7 of these hypotensive subjects. Another related a history of epistaxis monthly from fourteen to seventeen years of age when the menstrual flow was normally established. In their previous pregnancies there had been severe enough nausea and vomiting to confine seven of the women to bed for at least two weeks. The symptoms of effort-exhaustion cropped out often in the histories of the multiparous women, and one had had a quite severe anemia. Among the 21 labors, forceps had been used 11 times, version once and bag induction had been done 2 times with prolonged but spontaneous deliveries.

Nutrition and Weight.—In regard to nutrition and weights, as compared with the medicoactuarial tables for age and height, 20 of the women were from 5 to 15 pounds below normal, 10 from 15 to 35 pounds underweight, 13 were within 5 pounds of the calculated normal, and 7 were well overweight. This frequent finding of hypotension in association with underweight is well recognized as a common occurrence in the examination of large groups of individuals. Concerning the constitution and physical characteristics of these women, when one attempts to classify them by Mills's classification, there were no hypersthenics, 22 sthenics, 2 hyposthenics and 26 asthenics. In other words there was an almost equal division of these women into sthenics and asthenics. The overweight women were held to an average gain in the last six months of 11½ pounds, those who were underweight, in spite of free feeding, could not be raised to an average of over 13 pounds, this included one woman who gained 54 pounds during her twin pregnancy.

Blood Pressure.—At least 8 estimations of the blood pressure were made on each of these patients. The initial pressure readings of all women in the group averaged 92 systolic and 58 diastolic. No pressure exceeded 100 mm., except for the 1 woman who developed eclampsia. The average low pressure readings were 82 and 56, the average high pressures during the period of observation were 94 and 64; in 6 of the women the maximum pressure never rose above 90 mm. The relation of the systolic pressure to the diastolic pressure and the pulse pressure remained in the ratio generally accepted for normal cases, 3 to 2 to 1, instead of the more frequent ratio of 5 to 3 to 2 in some series of recorded observations on nonpregnant hypotensive individuals.

Physical Findings.—Examination of the heart showed that, in addi-

tion to the 4 patients who had been treated for cardiac disease before pregnancy began, there were 6 with mitral systolic murmurs, 1 with an aortic systolic murmur, and in 19 it was noted that there was a poor heart tone. Treatment of these patients with digitalis and strychnin produced no effect upon the blood pressure. Strychnin produced a sense of stimulation in some of them, and in some instances a slight rise always followed a course of strychnin. Ephedrine was given without success to 2 women, while pituitary gland did not show any effect upon the systolic pressure. The basal metabolic rate in 6 patients who apparently had hypothyroidism was within the normal limits, minus 10 to plus 5. In these and in several other similar instances thyroid gland was exhibited without any change in the pressure. In about half of the series, it appears from a graphic chart, there was a moderate rise in the systolic pressure at about seven and one-half months, this rise was not sustained, however, and may indicate that this time represented the acme of metabolic activity on the part of these women.

Symptomatology.—Anemia, of the so-called physiologic type of pregnancy, was frequently noted. Six women showed a hemoglobin of 75 per cent, and 13 a reading of below 75 per cent, with a reduction of the red cells to below 3,500,000. In none of the women was the pernicious type of anemia of pregnancy seen. There was administered to those with anemia various combinations of iron and arsenic by mouth or by hypodermic with variable results. The average low systolic pressure was 80 mm. In so far as the effect of this therapy upon the pressure was concerned there was an average rise of 10 points systolic and 12 points diastolic following treatment. So it may be assumed that intensive treatment of pregnancy anemias reflexly influences the cardiovascular mechanism. In no instance were positive Wassermann reactions obtained.

Dyspnea and fatigue were most frequent among the subjective symptoms; effort-exhaustion, headaches, sleepiness, and mental dullness were complained of by over half the patients. Attacks of mental depression and "nervous spells" were prominent subjective phenomena.

Toxemia appears relatively infrequently among these women, but 1 patient developed eclampsia, postpartum, after a rising blood pressure in late pregnancy, with albuminuria, for which a bag induction was done. This patient with an initial blood pressure at the second month of 90-60, had 100-60 at the thirty-sixth week. Two weeks later there was marked edema, albuminuria and the systolic pressure had risen to 120 mm., she had gained 54 pounds during the pregnancy in spite of remonstrances against her gross appetite, and as evidence of kidney involvement became more marked as induction was done. The labor was long and slow, twins were delivered by low forceps and version. Several convulsions developed during the first six hours after delivery with the blood pressure rising to 174-96 at one time.

The patient recovered, and the pressure quickly fell to its former low level where it has remained over a period of five years. Eight of the patients of the series developed definite albuminuria and edema of the ankles in late pregnancy without any rise in pressure. It appears that in at least one instance the definite rise from a hypotensive level was just as suggestive and prognostic of impending toxemia as a similar rise in a normal pressure individual, and such rise should not be regarded with equanimity. Several times when a reading was made immediately postpartum there was never a drop in the systolic pressure of over 10 points. The lowest systolic pressure recorded was 60 mm. with no evidence of shock.

Obstetric History.—Any constitutional inferiority as a causative factor in the production of the low systolic pressure was not reflected in a marked degree of pelvic infantilism as a stigma. In accordance with what one might expect from their physical configuration and stature 11 of the women showed justominor pelves. Two had generally contracted pelves, one a flat pelvis, and 2 had narrowing of the transverse diameter of the outlet. Five infants were delivered with low forceps, 6 with midforceps, cesarean section was done twice for contracted pelvis, and version once upon a twin. Breech extractions were done 3 times. The duration of labor showed an average of twelve hours for the multiparous women, thirty-one hours for the primiparous women and twenty-one hours for all labors in spite of the number of premature and forceps deliveries; in all a rather definite prolongation of the duration of labor as contrasted with normal labors.

The average weight of the babies born to primiparas was 6 pounds and 1 ounce, to the multiparas, 7 pounds and 4 ounces. Nine babies were born prematurely from four to eight weeks, 4 of them died; in addition one subnormal baby with both arms absent died during the first week, and an anencephalic monster died immediately after birth. Of the premature babies 2 weighed under 4 pounds and 4 under 5 pounds. It will thus be seen that in this series there was a tendency to lowered weight of the primiparas' babies, and a marked increase in the usual ratio of premature deliveries. Whether this is significant, or not, is speculative; it can hardly be proved that these results depended upon the finding of a low blood pressure in the mothers, but at least the results point to the mothers being substandard. The ability of these women to nurse their babies was quite poor, but 15 were nursing their offspring in whole or in part when they left the hospitals.

Follow-Up.—The follow-up on these women at their final examinations from four to twelve weeks after delivery, to several years later, showed an average blood pressure of 94 systolic, 66 diastolic, there had been a sustained rise in none of them. The average weight loss from the recorded maximum recorded, on the occasion of the final examination, was 17 pounds.

DISCUSSION

Hypotension, systolic pressure of 100 mm. or less, occurs among about 5 per cent of pregnant women in early adult life. Many of these patients showed a late development of sexual maturity as evidenced by delayed appearance of the menstrual flow. Hypotensive women do not seem to be quickly fertile after marriage, and it is possible that this etiologic cause of delayed pregnancy may also be a factor among other sterile women who frequently present a hypotension.

One-fifth of the number of patients studied had had severe attacks of influenza within recent years. Other infectious diseases had occurred in about the usual frequency. Definite cardiac disease or weakness, and presumable myocardial insufficiency, was present in nearly half the patients. Tuberculosis was definitely present in 1, suggestively in 4. Degrees of ptosis of the abdominal organs were found in one-sixth of the women, some of whom had had symptoms sufficient to warrant treatment.

Of the women who were first seen after passing through one or more pregnancies, there was a history of one-fourth having had marked nausea and vomiting. The ratio of miscarriages was well above normal. The symptom-complex, fatigue-exhaustion was often noted, the labors had been long and ended by an unusually high number of operative deliveries.

Underweight was noted in 60 per cent of the patients studied, which finding corresponds to other correlated studies of weight and blood pressure. An attempt to classify this series of patients according to their physical characteristics resulted in dividing them into two groups, the sthenic and the asthenic, with a slight preponderance of the latter. When this grouping was compared with the nutrition analysis most of the underweight women fell into the asthenic group. There was an almost total absence in this series of that type of woman described by Draper[18] as being subject to the cardiovascular hypertensive type of toxemia of pregnancy. The difficulty of building up these undernourished and asthenic individuals may be seen from the fact that an average of but 13 pounds, including 1 gain of 54 pounds, could be added during the last 2 trimesters in face of what in some examples amounted to forced feeding.

The blood pressure readings showed a definite hypotension, and the average readings ranged from a low of 82 over 56 to a high of 94 over 64. In about half the cases a graphic chart showed a rise up to about the thirty-fifth week, which may have represented the acme of metabolic activity on the part of these women. The ratio of systolic, diastolic and pulse pressure remained in a normal ratio, 3 to 2 to 1. Treatment of cardiac conditions, or of the apparently weak myocardial muscle, by strychnin or digitalis did not have any sustained effect upon the systolic pressure. Other drugs, as ephedrine, thyroid and

pituitary, seemed of no effect. Treatment of the anemia, of the so-called physiologic type, in 26 per cent of the patients showed an apparent sluggishness on the part of the hematopoietic system. There was but a slight bettering of the anemia and a moderate rise in the pressure consequent upon the treatment.

These women complained in a degree quite above normal of physical inability, dyspnea and headaches while vertigo, mental dullness and psychic depression were frequently recurring subjective symptoms.

Aside from a few mild albuminurias with no coincident rise of pressure but one case of definite toxemia developed. This was no doubt a metabolic upset consequent upon an enormous gain in weight, eclampsia developing postpartum, after an induced twin labor, with recovery, and an early return, with persistence, to the former low systolic pressure. A rising systolic pressure is undoubtedly as significant of impending toxemia here as in a case with normal pressure. These women are almost wholly the very antithesis of the type developing the hypertensive form of toxemia of pregnancy.

The duration of labor showed quite an increase in the time usually required for normal spontaneous deliveries. In multiparas the average was twelve hours, in primiparas thirty-one hours, for all labors, including operative deliveries, twenty-one hours. Forceps were used 11 times, section was done twice, and version once, upon a second twin. The delay in the labors from a study of the histories was apparently equal for the two stages, and may be taken as an indication of the inability of the hypotensive type of woman to normally complete her physiologic task. There was an equally marked reflection of this inability in the larger proportion than usual of premature babies, 9 being born from four to eight weeks prematurely. The average weight of the baby born to the primiparous woman, 6 pounds and 1 ounce, may again reflect upon an originally poor germ plasma, as might also the two abnormal infants, one an anencephalus. The primiparous woman was as little able to nurse her infant as the multiparous, but 15 women were nursing their babies, in whole or in part, at the end of two weeks.

Estimation of the blood pressure and weight weeks or months after delivery showed that the stimulus of the metabolic activities of pregnancy had had no effect upon nutrition or the cardiovascular mechanism, the blood pressures persisting at their former low levels. There did not seem to have been any more marked tendency to errors of involution or to displacements than in the normal woman.

SUMMARY

Definite hypotension occurs in 5 per cent of pregnant women. These women often mature late and are relatively infertile. A certain proportion of them have had influenza, have weak cardiac musculature or

have an anemia. They are often of an asthenic build, as frequently underweight, and are difficult to build up. Treatment by various measures uniformly fails to raise the blood pressure appreciably. Their pregnancies are characterized by a high percentage of miscarriages and premature labors. Their children are smaller than normal. They complain greatly of effort-exhaustion, dyspnea, headaches and nervous depression. Tendency to toxemia is relatively slight. They suffer from prolonged labors, characterized by inertia, and operative interference is much more frequent than in normal women. They are largely unable to nurse their babies. The stimulus of pregnancy has no effect later on of raising the blood pressure.

Low arterial pressure in such patients may be but an expression of a constitutionally inferior, physically and in a reproductive sense, type of woman, and is often significant of her obstetric unfitness.

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BASAL METABOLISM STUDIES IN NORMAL PREGNANT WOMEN WITH NORMAL AND PATHOLOGIC THYROID GLANDS

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IT IS generally agreed that there is a definite increase in the basal metabolic rate during the latter part of normal pregnancy, but that this increase is "due to the increasing mass of active protoplasmic tissue, consisting of a large part of the fetal tissues and in lesser part of maternal structures" (Sandiford and Wheeler[1]), and is very moderate in extent. This argument is supported by the fact that subtraction of the calculated heat production of the fetus from the total heat production of the pregnant woman leaves the metabolic rate of the latter unaffected by gestation, and by the observation that almost immediately after delivery the metabolic rate falls to a point corresponding with that obtaining in early gestation or before conception.

When expressed in terms of the Aub-Dubois prediction standards, the total increase due to the rapid metabolism in the fetal tissues rarely amounts to more than 15 per cent. If one accepts the statement of Benedict[2] that all prediction standards are 5 per cent too high for normal women, the normal metabolic rate would range from minus 15 to plus 5 per cent according to the standards now in use. Using an increase of 15 per cent during pregnancy as the maximum which may be attributed to an augmentation of the active protoplasmic mass, it would be reasonable to view as potentially abnormal any rate above plus 20 per cent. However, Gustafson and Benedict[3] insist that even among 10 presumably healthy individuals at least one or more "will have a metabolism deviating more than plus-minus 10 per cent from the standards." This would lead one to anticipate readings of slightly higher or lower values in 10 to 20 per cent of any series. Mussey, Plummer, and Boothby[4] say that "a basal metabolic rate of plus 25 or even plus 30 is not necessarily an indication of hyperthyroidism in the latter months of pregnancy," and thus recognize the occasional variations pointed out by Gustafson and Benedict.[3] It would seem to be well demonstrated that a high basal metabolic rate unsupported by clinical evidence of hyperthyroidism does not warrant a diagnosis of abnormal thyroid activity.

In order to add further confirmation to the various previous reports on the basal metabolism of normal pregnant women with normal thyroid glands, and to investigate the metabolism in various varieties of

thyroid hypertrophy, we have studied 72 women through gestation and for several weeks after delivery. Our patients divide themselves into four groups, according to the clinical condition of the thyroid gland.

Normal thyroid gland	21 cases
Small colloid (endemic) goiter	23 cases
Adenomatous goiter	18 cases
Large colloid (visible) goiter	10 cases

Clinical differentiation of patients was made at their first visit to the clinic, upon the basis of careful palpation. Additional clinical observations were made at monthly intervals during pregnancy, and more frequently in the puerperium. All metabolism tests were made by the regular laboratory technicians as a part of their routine work. Aub-Dubois standards were employed and the technic outlined by Boothby and Sandiford[5] was followed in detail, the patients coming to the laboratory between eight and nine o'clock in the morning, the last food having been taken the preceding evening. Tests were made at four-week intervals, usually from the fourth lunar month. After delivery, two or three determinations were obtained during the first two weeks and another, if possible, at six weeks. The results of tests which were for any reason unsatisfactory were discarded, accounting for various breaks in the series. Private patients alone were utilized and full cooperation was demanded. A predominance of primiparous women is explained by the fact that it is generally easier for them to keep early morning appointments.

NORMAL PREGNANCY: NORMAL BASAL METABOLIC RATE

Compilation of the results showed that in each group there were numerous patients who had unquestionably normal metabolic rates which never rose above plus 20 per cent. Such determinations upon 48 individuals have been combined in a single chart (Fig. 1) with the median shown by the heavy dotted line. The average increase in the basal metabolic rate is from plus 1 per cent in the third to plus 9 per cent in the tenth lunar month, while during the first week after delivery the rate falls to plus 1, the early pregnancy point. In the later puerperium, there is a progressive slight fall to an average of minus 7 per cent during the third week. This curve is consistent with the results of previous workers (Sandiford and Wheeler,[1] Rowe, Alcott and Mortimer,[6] Root and Root,[7] etc.), and confirms the observation that lactation is not associated with an increased metabolism. Diminished physical activity has been held largely responsible for this observed postpartum fall in the basal metabolic rate.

Utilizing other data obtained when the metabolism tests were made, it was possible to construct the curves for average variations in weight, pulse, and blood pressure, as well as for the metabolic rate. The general similarity of the curves as plotted is striking. The weight

shows an average gain during pregnancy of 17 kg. (37½ pounds), with a loss at delivery of 9 kg. (20 pounds), and an apparent permanent gain to the body of 8 kg. (17½ pounds). There is a slight increase in the pulse rate as pregnancy advances, with a drop to normal shortly after delivery. The blood pressure tends to be low early in gestation, but undergoes a rise in the last month, and a slow fall during the puerperium.

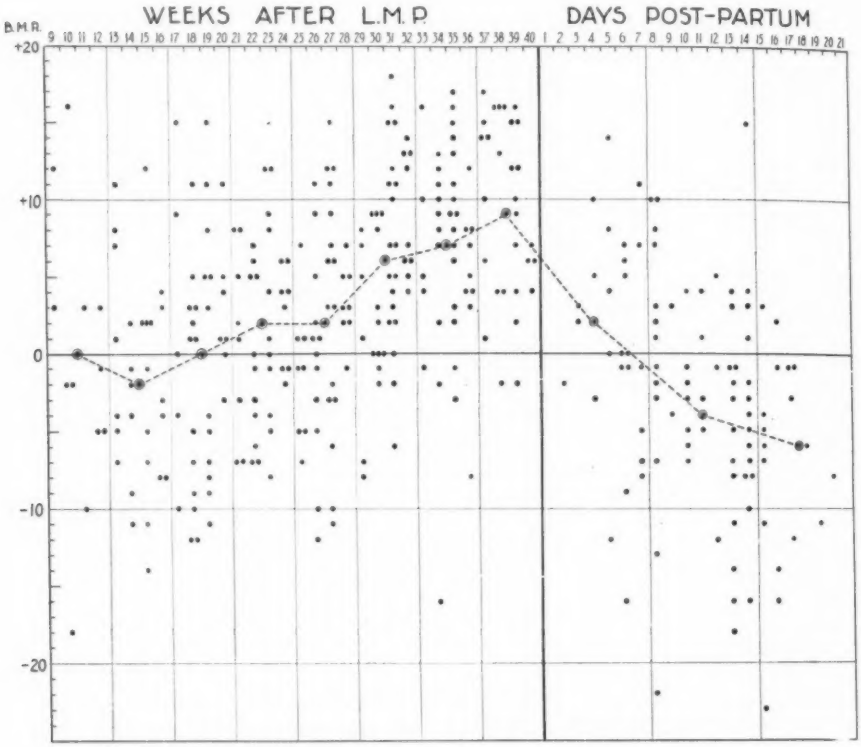

Fig. 1.—Basal metabolic determinations among 48 normal pregnant women with normal thyroid activity. Each dot represents a single satisfactory reading.

Twenty-two of the patients in this group were given sodium iodide (4 grains per day for ten days) at intervals of two or three months throughout the pregnancy, 9 patients used iodine salt exclusively during gestation, and 17 had no iodine added to the diet. It cannot be shown that the use of iodine was reflected in the metabolic rate. Examinations of the thyroid glands of the newborn babies, however, revealed that among the 17 women who had no prophylactic iodine, 5 gave birth to babies with appreciably enlarged thyroids, whereas congenital goiter was not noted in any instance where the mother took iodine.

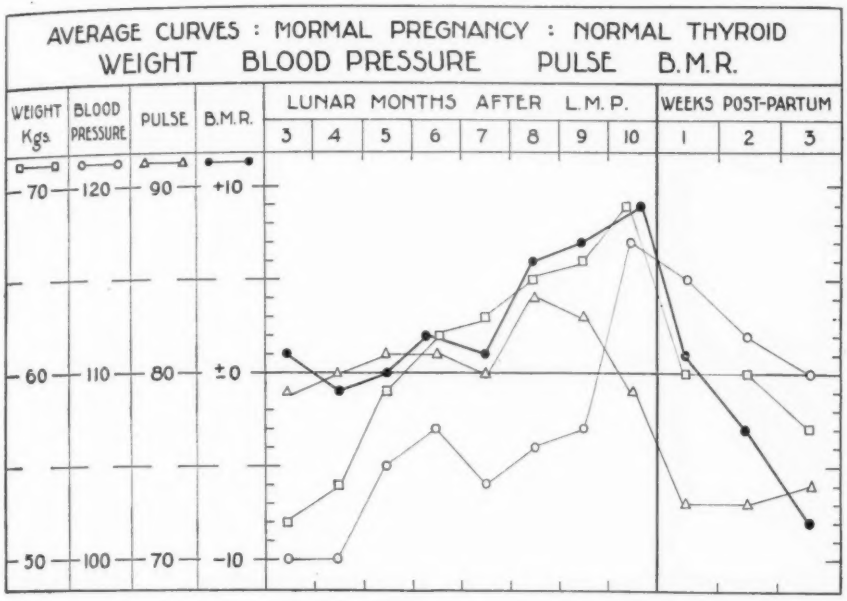

Fig. 2.—Average pregnancy changes in pulse, blood pressure, weight, and metabolic rate as deduced from data on 48 normal pregnant women.

NORMAL PREGNANCY: INCREASED BASAL METABOLIC RATE

Twenty-four (33 per cent) of the 72 patients studied showed metabolic rates above the chosen standard of plus 20 per cent on one or more tests, and were subjected to closer study. The distribution of these cases among the various clinical groups was as follows:

THYROID GLAND	NORMAL B. M. R.	B. M. R. ABOVE PLUS 20	TOTAL
Normal	16	5 (24%)	21
Small colloid goiter	15	8 (35%)	23
Adenomatous goiter	12	6 (33%)	18
Large colloid goiter	5	5 (50%)	10

Palpable evidence of thyroid hypertrophy is apparently associated with a greater tendency toward increased metabolism, as might well be expected. Our work does not, however, support the inference to be drawn from the report of Davis,[8] that all normal pregnant women who have thyroid hypertrophy show metabolic rates above normal.

The patients with increased metabolic rates (above plus 20 per cent) will be discussed separately according to the type of gland hypertrophy present.

NORMAL THYROID GLAND: INCREASED BASAL METABOLIC RATE

Five of 21 patients with normal thyroids had rates above plus 20 per cent, an incidence which is hardly above the average expectancy of increased metabolism. The great preponderance of plus readings should, however, be noted, with the tendency toward early pregnancy

values well above the average. On the other hand, it will be seen that after delivery the values are comparable with those of early pregnancy, with a decided second-week drop, which does not go below the zero line. The average increase during pregnancy is 15 per cent and the average first-week postpartum drop is 12 per cent. These curves follow the usual course but in each case the metabolism is constantly slightly above the average. Two of the patients, Cases 17 and 18, showed a definite pregnancy enlargement of the thyroid gland; two others, Cases 19 and 21, complained of increasing nervousness and presented tremors, while only one (Case 20) had no clinical evidence of thyroid change. In no case were the symptoms sufficiently marked to demand treatment, but it would seem that such individuals must be in a state of potential hyperthyroidism as a result of the pregnancy increase of metabolism.

NORMAL THYROID : NORMAL PREGNANCY : INCREASED B.M.R.

CASE NO.	AGE	PARITY	IODINE	WEEKS OF PREGNANCY								WEEKS AFTER DELIVERY						HYPER-THYROID-ISM.
				3	4	5	6	7	8	9	10	1	2	3	4	5	6	
17	21	I	Na I 20, 28		+15		+5	+12	+15	+27	+25		+6					0
18	28	I	NaI 16, 24, 32	+4	+5	+10		+17	+2	+21		+12	-5					0
19	31	I	I. S.		+15	+20	+14	+18	+22	+29		+13	+5				±0	0
20	27	I	I. S.			+4	+10	-3	+12	+16	+24			+8				0
21	34	II	0						+24	+33	+30	+18	+14				+2	+

Fig. 3.—Basal metabolic rates in 5 normal pregnant women with normal-sized thyroid glands but with increased metabolism.

CASES 17 and 18, when examined two weeks postpartum, had symmetrical enlargements of the gland, which had not been noted previously, but signs of hyperthyroidism could not be elicited. Both infant thyroids were normal, due probably to the protection afforded by the sodium iodide administered during pregnancy. We feel that in these instances the thyroid enlargements were gestational phenomena.

CASES 19 and 20 showed no enlargement of the thyroid at any time. Iodine salt was used throughout the pregnancies. The infant thyroids were not enlarged. Patient No. 19 was unusually nervous and might be designated a hyperthyroid type, although clinical evidence of hyperthyroidism was not present.

CASE 20 had symptoms somewhat suggestive of very early exophthalmic goiter with characteristic eye signs and general nervousness, although the pulse rate was normal and no enlargement of the thyroid could be determined. No iodine was given during pregnancy. The infant had a congenital goiter, which led us to believe that the maternal thyroid function was abnormal and that the elevated metabolism was probably due to mild hyperthyroidism. Further study and a metabolism test one year after delivery failed to make a positive diagnosis, although the symptoms had persisted.

SMALL COLLOID (ENDEMIC) GOITER: INCREASED BASAL METABOLIC RATE

For the purpose of this study, an endemic colloid goiter is defined as a thyroid gland whose isthmus is distinctly enlarged but estimated to be not more than 2.0 cm. thick, and whose lobes show a palpable, sym-

metrical enlargement. In making such a diagnosis, the possibility of pregnancy hypertrophy had to be considered, but since the initial examination was usually made before the sixteenth week of pregnancy, when gestational hypertrophy is making its appearance, it is felt that these are instances of true endemic enlargement. The fact that our observations were carried out in a region of endemic goiter supports that view. Among the 23 patients in this group, there were 8 who showed metabolic readings above normal. (Fig. 4.)

In the majority of these patients, the metabolic readings in early pregnancy were above normal, and only Case 43 had a normal postpartum metabolism. In this case there was a twin pregnancy and in all probability the increased bulk of fetal protoplasm was responsible for the unusual rise in the metabolic rate. Cases 40 and 41 showed par-

SMALL COLLOID GOITER : NORMAL PREGNANCY : INCREASED B.M.R.																	
CASE NO.	AGE	PARITY	IODINE	WEEKS OF PREGNANCY								WEEKS AFTER DELIVERY						HYPER-THYROID-ISM.
				3	4	5	6	7	8	9	10	1	2	3	4	5	6	
37	23	I	NaI 28, 36					+3	+21	+24	+9	+7	+5	+3				0
38	25	II	NaI 18, 24	+10	+3	-1	+18	+10		+21		+12	+15				+4	+
39	30	I	NaI 20, 32			+4		+6	+22	+32	+37		+27	+13			-2	+
40	31	I	NaI 13, 21, 34	+24		+11	+11	+12	+7	+25			+7					0
41	21	I	NaI 20		+27	+17	+9	+14		+28	+5	+14	+10					0
42	28	I	NaI 20, 28		+5	+9	+9	+32		+25		+15	+8					±
43	30	I	I. S.			-3	+12		+20	+16	+24		+2	-2				0
44	25	II	0		-2	+4		+7	+14	+24	+7	+12	+7					0

Fig. 4.—Basal metabolic rates in 8 normal pregnant women with endemic goiters and with increased metabolism.

ticularly high metabolism in the early months and relatively little increase as gestation progressed, with postpartum values below those in early pregnancy. Both patients received prophylactic iodine, which may have served to protect them from developing a much more rapid metabolism in the latter part of pregnancy, although our general experience would hardly warrant such an hypothesis. On the other hand, Cases 39 and 44 showed pregnancy increases of metabolism of 33 and 26 per cent, respectively, and following delivery had metabolic readings well above their early pregnancy values. It would seem that gestation had served to stimulate thyroid activity to some extent without leading to clean-cut symptoms and signs of hyperthyroidism.

These 7 cases, excluding No. 43, all gave positive or quite suggestive evidence of increased thyroid activity during pregnancy. The fact that they showed a return of the metabolic rate to normal during the puerperium, even though it was markedly delayed, leads us to feel

that the increased thyroid activity may well have been due to a stimulation of thyroid function brought about by the pregnancy.

CASE 37.—There was no increase in the size of the thyroid and no definite clinical evidence of hyperthyroidism was noted during the period of observation. The infant thyroid was normal in size.

CASE 38.—No increase in the size of the thyroid was noted during pregnancy. The infant thyroid was normal in size. Clinically, there were symptoms of a mild hyperthyroidism, fine tremor, tachycardia, and nervous manifestations.

CASE 39.—The thyroid showed a slight increase in size in late pregnancy which persisted into the puerperium. Clinical evidence of mild hyperthyroidism was present in the latter months of gestation and was especially noticeable after delivery. The infant thyroid was normal.

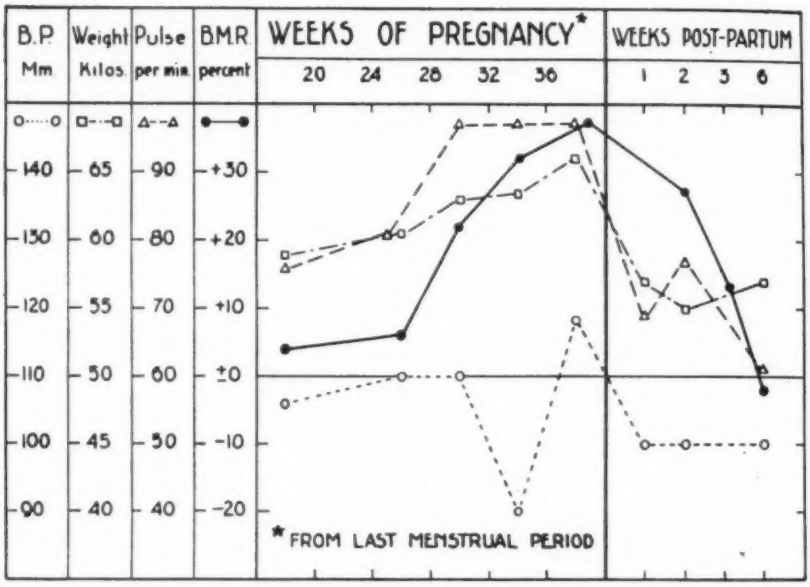

Fig. 5.—Case 39. Small colloid goiter showing definite, temporary thyroid hyperthyroid activity during pregnancy.

CASE 40.—This patient was of a neurasthenic type and was underweight at the beginning of pregnancy. During gestation there was a considerable gain in weight and a marked improvement in general health. There was a history of a slight hyperthyroidism, which had been treated medically some years previously. The thyroid did not increase in size appreciably during pregnancy, and no evidence of hyperthyroidism could be found. The infant thyroid was normal.

CASE 41.—Enlargement of the thyroid gland was first noticed at puberty, when a short course of iodine treatment was given. During pregnancy the gland did not increase in size, and there were no positive clinical signs of hyperthyroidism. The infant thyroid was normal.

CASE 42.—There was no previous history of goiter, and no increase in size of the gland was noted during pregnancy. Clinical evidence of hyperthyroidism was

lacking, except that the patient had a slight tachycardia, which persisted through pregnancy and the puerperium. The infant thyroid was normal.

CASE 43.—Twin pregnancy. Some thyroid enlargement was first noticed at the time of puberty, but was not treated. During gestation there was no apparent enlargement of the gland and there were no clinical signs of hyperthyroidism. The increased metabolism is probably explained by the multiple pregnancy. After delivery the curve fell rapidly to normal. The infant thyroids were not enlarged.

CASE 44.—The goiter probably dates from puberty. There was no enlargement of the gland during this pregnancy nor during the first gestation two years previously. No signs of hyperthyroidism. The infant thyroid was normal.

ADENOMATOUS GOITER: INCREASED BASAL METABOLIC RATE

All patients who showed palpable adenomas of the thyroid are grouped in this section. Since the determination was entirely clinical, it is possible that other small adenomas were missed and the patients placed in other groups. Of the 18 patients who had definite adenomas,

ADENOMATOUS GOITER : NORMAL PREGNANCY : INCREASED B.M.R.

CASE NO.	AGE	PARITY	IODINE	WEEKS OF PREGNANCY								WEEKS AFTER DELIVERY						HYPER-THYROID-ISM.
				3	4	5	6	7	8	9	10	1	2	3	4	5	6	
57	31	I	0	+10	+4	+10	+11	+15	+19	+22	+25	+4	-1				-2	0
58	27	II	NaI 14, 28		+2	+10	+17	+23			+30	+26	+19	+18			+10	+
59	31	III	NaI 18, 24			+10	+15	+15	+25	+35		+21	+2				-6	+
60	41	II	NaI 10	+32	+41	+50	+29	-1	-5			-14		-11			-29	+++
61	28	I	0		+10	+5	+10	+8	+13	+28	+17	+14	±0				-2	++
62	37	I	0	+8	+15		+6	+27		+18	+34	+14	+15				+4	+

Fig. 6.—Basal metabolic rates in 6 normal pregnant women with adenomatous goiters and with increased metabolism.

6 had metabolic rates above plus 20 per cent together with clinical evidence of hyperthyroidism, except one case, and will be considered separately.

In general the rise in the metabolic rate during pregnancy is greater than in normal individuals and the postpartum drop is slower and less complete. Only one patient (No. 62) showed a definite increase in size of the gland during gestation. Three patients had prophylactic iodine and 3 were not treated. Among those who received sodium iodide, there was no evidence of congenital goiter in the newborn even though the thyroid enlargement was greater and the basal metabolic rate higher than in the other 3 who were given no iodine, and among whom there were two instances of congenital goiter in the infants. Only in Case 60 was there any reason to believe that iodine might have done harm and here the metabolic rate was considerably elevated (plus 32 per cent) before sodium iodide was administered, about the tenth week, when clinical symptoms of hyperthyroidism were already gradually increasing.

CASE 57.—No history of the time of appearance of the goiter could be obtained; there had been no previous treatment. There were no definite clinical signs of hyperthyroidism, and no increase in the size of the thyroid or of the adenoma was detected during pregnancy. The patient received no iodine therapy; the child showed a small congenital goiter.

CASE 58.—The goiter was first noticed at the time of puberty and some iodine therapy was employed at that time. At the third month of pregnancy, there was a visible goiter with adenomas in each lobe and clinical signs of a mild hyperthyroidism. Following sodium iodide (4 grains q.d. for ten days) in the fourth month of pregnancy, there was a slight decrease in size of the glands, with no further increase during the latter months of pregnancy. The metabolic rate was still above normal (plus 10 per cent) six weeks after delivery. The infant thyroid was normal.

CASE 59.—The goiter had been present for several years, enlarging during each pregnancy, but no definite history of its first appearance could be obtained. One year before the onset of this pregnancy medical treatment had been given and operation advised but refused. At the fourth month of gestation there was a visible goiter with multiple adenomas, and evidence of a slight hyperthyroidism with fine tremor, tachycardia, and nervous irritability. Sodium iodide was given during the fifth and the seventh lunar months and was followed by improvement of the symptoms. There was no change in the size of the gland during pregnancy. The infant thyroid was normal.

CASE 60.—The history of the appearance of the goiter is uncertain but the enlargement had been noted for some years, although the story did not suggest hyperthyroid symptoms. The patient was admitted to the hospital when nine weeks pregnant because of nausea, which was treated successfully by the usual suggestive therapy. When the vomiting ceased, a course of sodium iodide was given. During the next two months the symptoms of hyperthyroidism increased steadily and at the nineteenth week the patient was again hospitalized. Three weeks of bed rest together with the administration of Lugol's solution daily effected no improvement (very possibly the iodine was harmful) and finally at the twenty-second week a subtotal thyroidectomy was performed. After a stormy, early postoperative course, convalescence proceeded normally and the pregnancy continued uneventfully to term. After delivery a mild myxedema appeared and was treated with thyroid extract. The infant thyroid was normal.

CASE 61.—There was no history of onset of the goiter; no previous iodine treatment had been given. The thyroid increased definitely in size during pregnancy, and in the latter months there developed signs of hyperthyroidism (tremor and nervous manifestations), which persisted into the puerperium. The infant thyroid was moderately enlarged. This case seems to illustrate quite well the possible effect of pregnancy upon a thyroid gland which is not quite normal when gestation begins. Iodine therapy might have prevented the development of symptoms.

CASE 62.—The onset of the goiter was not noted; there had been no previous iodine treatment. Examination at the second month of pregnancy showed a palpable enlargement of the thyroid with a small adenoma in one lobe. No iodine treatment was given during pregnancy. The gland showed a definite enlargement during gestation. Late in pregnancy and during the puerperium there developed clinical signs of hyperthyroidism in the form of a fine tremor and various nervous manifestations. The infant showed a congenitally enlarged thyroid. After delivery, the metabolism remained elevated with a slow return to normal. The patient illustrates the train of signs and symptoms which pregnancy may produce in the presence of a goiter.

LARGE COLLOID GOITER: INCREASED BASAL METABOLIC RATE

One-half of the large colloid goiter group developed elevated metabolic rates together with signs of hyperthyroidism, while the other 50 per cent pursued a course unaffected by gestation. The elevation of metabolism in the first 5 cases can, in all probability, be attributed to hyperactivity of the thyroid. Two of these patients had no prophylactic iodine during pregnancy and both infants were born with congenital goiters. Assuming that the rate of metabolism postpartum is an index of the activity of the thyroid, these patients all suffered from a mild hyperthyroidism. Colloid goiters frequently have little active thyroid tissue and the increased demands of pregnancy may well be expected to lead to an abnormal activity with resultant evidence of thyroid intoxication.

CASE 68.—The goiter was first noticed at the time of puberty and some iodine was given at that time. At the fourth month of pregnancy there was a visible enlargement of the thyroid and clinical symptoms of a mild hyperthyroidism. The first course of sodium iodide at the fifth month was followed by a slight decrease in the size of the gland, with no further change apparent during the remainder of pregnancy. The infant thyroid was unaffected.

LARGE COLLOID GOITER : NORMAL PREGNANCY : INCREASED B.M.R.

CASE NO	AGE	PARITY	IODINE	WEEKS OF PREGNANCY								WEEKS AFTER DELIVERY						HYPERTHYROIDISM.
				3	4	5	6	7	8	9	10	1	2	3	4	5	6	
68	29	I	NaI 17, 28			+14	+3	+15	+10	+23	+30		+5				+3	+
69	32	V	NaI 32						+19			+24				+12		0
70	30	III	NaI 15, 23	+23	+17	+30		+45	+31	+53	+50	+20	+23				+5	+
71	33	I	I. S.			+ 9		+23		+29		+23	+9				+31	±
72	24	I	0		-1	+7	+20	+29	+25	+44				+2				±

Fig. 7.—Basal metabolic rates in 5 normal pregnant women with large colloid goiters and with increased metabolism.

CASE 69.—The goiter was first noticed during puberty, and the patient received some iodine treatment at that time, but none later. An operation, probably ligation of the vessels, was done on the thyroid seven years previously. At the eighth lunar month of pregnancy, when first seen, there was a large symmetrical colloid goiter, which filled the front of the neck and gave slight evidence of pressure upon the trachea. There was no definite clinical evidence of hyperthyroidism. Sodium iodide was given during the ninth lunar month but did not protect the fetal thyroid which was somewhat enlarged at birth.

CASE 70.—The goiter dated from puberty when some iodine treatment was given. Examinations at the third lunar month showed a large, lobular, colloid goiter (Fig. 2), with evidence of mild hyperthyroidism. Sodium iodide given during the fourth and sixth lunar months did not affect the size of the gland, but did protect the fetal thyroid which was normal at birth.

CASE 71.—Onset of the goiter at puberty; no previous iodine treatment. Examination at the fifth lunar month of gestation showed an easily visible symmetrical

enlargement of the thyroid but no evidence of even mild hyperthyroidism. Sodium iodide given at the sixth month was followed by a definite decrease in the size of the gland, which showed no further change during pregnancy. The infant thyroid was normal.

CASE 72.—The patient does not know when the goiter first appeared; there had been no previous iodine treatment. Examination at the third month of pregnancy showed visible enlargement of the thyroid gland with no evidence of hyperthyroidism. Iodine was not administered during gestation and the goiter exhibited a palpable increase in size as pregnancy advanced. The infant thyroid was congenitally enlarged.

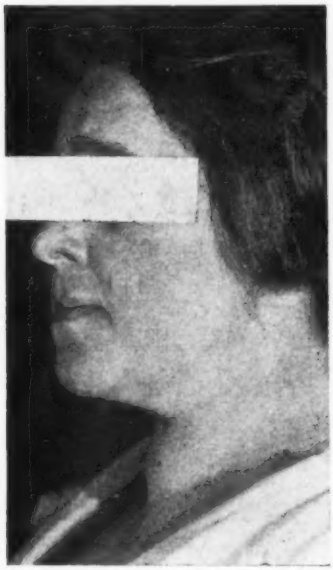

Fig. 8.—Case 69. Large colloid goiter.

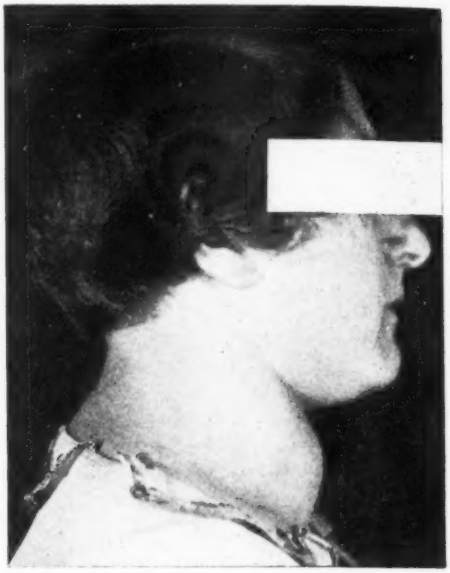

Fig. 9.—Case 70. Large colloid goiter.

DISCUSSION

These studies would seem to indicate that pregnancy tends to place upon the thyroid gland an extra burden, which the perfectly normal gland is able to assume without great difficulty, but which causes certain disturbances in those individuals whose thyroids are already somewhat affected when gestation begins. The greater the original pathologic alteration in the gland, the greater the chance that pregnancy will lead to true hyperthyroidism. The determination of hyperthyroidism is a clinical problem but basal metabolic estimations are useful diagnostic adjuncts when interpreted correctly. An unusual increase in the metabolic rate during pregnancy, together with an early postdelivery reading above the early-pregnancy value and a slow return of the metabolism to normal, can best be interpreted as indicating a true pregnancy hyperplasia of the thyroid. Our conclusions in this regard agree with those reached by Davis.[7]

The use of prophylactic doses of iodine during pregnancy apparently has but little effect in preventing gestational hypertrophy of the thyroid (Cases 17 and 18), provided the gland is of normal size originally, but it is useful in preventing such an hypertrophy in colloid goiters and may even lead to a decrease in their size. (Cases 68 and 71.) The first of these statements is in contradiction to Davis,[7] who believes that "if a woman with a normal thyroid takes sufficient iodine during the course of a normal pregnancy, her basal metabolic rate will remain within normal limits, although it may show a gradual increase during the last weeks of pregnancy." Our different results may be due to the fact that we did not use the same method for giving the iodine, and that our procedure of giving occasional saturation doses of sodium

THE EFFECT OF IODINE PROPHYLAXIS ON THE INFANT THYROID

MATERNAL THYROID	SODIUM IODIDE			IODINE SALT			NO IODINE		
	NO. OF INFANTS	ENLARGED GLAND		NO OF BABIES	ENLARGED GLAND		NO. OF BABIES	ENLARGED GLAND	
		NO	PERCENT		NO.	PERCENT		NO.	PERCENT
NOT ENLARGED	50	9	18	121	4	3	79	40	50
SLIGHTLY ENLARGED (ENDEMIC COLLOID)	53	14	26	78	4	5	60	28	47
ADENOMATOUS GOITER	30	3	10	16	1	7	10	5	50
LARGE COLLOID GOITER	37	14	38	28	2	7	12	7	60

Fig. 10.—The effect on the infant thyroid of iodine given prophylactically to the mother during pregnancy.

iodide may not be adequate. None of our patients who depended upon iodine salt exhibited any hypertrophy of the thyroid, but the series is too small to be significant.

In no instance, except possibly Case 60, was there any indication that the use of iodine had done harm, and our experience during the past seven years has failed to develop such cases. However, in view of the experiences of Mussey, Plummer, and Boothby[4] and of Falls,[9] this possibility must be admitted and adequate precautions taken to avoid serious consequences, but we cannot believe that it should be used as an argument against the use of iodine routinely in pregnant women. We believe that the amount of good to be derived from such prophylactic medication by both the mother and her infant more than balances the possible harm in the occasional patient.

The protective effect upon the fetal thyroid of iodine administered to the mother during gestation adds a considerable argument in favor of such prophylaxis.[10] Among a group of more than 500 consecutive pregnancies studied clinically, the observations upon the condition of the infant thyroid were made as shown in Fig. 10.

Such a tabulation shows that without prophylactic iodine approximately one-half of all babies born in a region of endemic goiter will show some thyroid enlargement, but that under any form of iodine administration the incidence is considerably diminished, with iodine salt being, apparently, particularly effective.

CONCLUSIONS

1. The basal metabolic rate shows an increase during normal uncomplicated pregnancy of approximately 15 per cent, with a fall to normal in the first few days after delivery. A greater rise with slower fall to normal suggests increased thyroid activity incident to pregnancy.

2. A small percentage (in our series 20 per cent) of women with clinically normal thyroid glands have a metabolic rate which rises above plus 20 per cent. Patients with palpable thyroid disease show a greater tendency toward such high rates, the incidence rising to 35 per cent with small colloid and adenomatous goiters, and to 50 per cent in the large colloid type. This is taken to indicate that pathologic thyroid glands are less able to respond normally to the demands of gestation, but tend to function abnormally and so to produce symptoms of hyperthyroidism.

3. Iodine, given prophylactically during pregnancy, is apparently unable uniformly to prevent gestational hypertrophy of the normal thyroid gland, but seems to be quite effective in preventing such a change in glands which are pathologically altered when pregnancy begins, and may actually lead to a reduction in the size of certain colloid goiters.

4. Iodine given to pregnant women acts very effectively to prevent the appearance of congenital goiter in the newborn.

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HOOKWORM DISEASE AND PREGNANCY

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HOOKWORM disease, caused by Ankylostoma duodenale or by Necator americanus, is found, according to Dock and Bass,[1] in all parts of the tropics, in many subtropical countries, and also in some temperate regions. It has, in all probability, existed from time immemorial, though its exact identity has been established and the causative agent isolated only in the past half century. It is characterized chiefly by an anemia of varying intensity, dependent upon the severity of the infection, with a concomitant state of mental and physical languor, rendering the subject more or less incapable of performing properly his appointed tasks, and hence is directly responsible for a great deal of economic inefficiency and waste. It is essentially a soil pollution disease, and thus affects particularly those whose work brings them into intimate relations with the soil, such as farmers and farm laborers, miners, etc. In our country it is found chiefly in the southern states, and in some areas it is responsible for severe economic losses. Some patients are heavily infected and are incapacitated, the majority have mild or moderate infestations and are not acutely ill, but are tremendously handicapped, while those with very light infestations are of considerable importance as carriers.

The disease may be contracted by ingestion of the ova with the food, but it is well established that the chief route of infection is through the skin, generally that of the feet, the initial lesion being commonly referred to as "ground itch." Going barefoot in infested areas is hence the usual way in which the malady is acquired. The infested mud is particularly prone to lodge between the toes; the encysted larvae dig their way into the skin and deeper tissues, reach the blood stream, then are carried to the right heart and thence to the lungs. Here they are entrapped in the capillaries because of their size, penetrate the tissues, and get into the bronchial tubes. Next they reach the mouth and pharynx, being carried there by the constant outward current of the mucous membrane or by coughing, and are swallowed. An astute Mexican observer, P. H. Lira,[2] has described this cough as a symptom of hookworm disease, and has reported cases erroneously diagnosed as tuberculosis in this stage of the infection. Dock and Bass also mention this cough as one of the symptoms. Reaching the small intestine, the larvae undergo further metamorphosis, and anchor themselves by means of their hooks, to the mucous membrane, chiefly of the duodenum and upper jejunum. Loss of blood ensues from the bites of the

worms; some of this blood is ingested by the parasites, some can be found in the feces by appropriate tests. There is some evidence suggesting that the worms also feed on intestinal mucus and on the mucosa. Bacterial infection of the bites occurs, and plays an important part in the pathology of the disease. Some observers believe that a specific toxin is in some way elaborated and absorbed. Ova produced by the female worms are constantly being cast off, but do not hatch into larvae in the intestine of the host; this occurs in the warm, moist soil after the eggs are passed in the feces. The persistence of the disease is maintained in great part by reinfection; Chandler[3] believes "that there is a rapid loss of the parasites and an equally rapid replacement by new ones." Both he and Bass believe, however, that some parasites may live in the intestine of the host for as long as six or seven years. One of my patients had been living in the city for five years, with little or no opportunity for reinfestation in the usual manner, but still harbored the worms.

The symptomatology naturally varies with the degree of the infestation. The severe cases present objective symptoms, the milder ones frequently do not, so that these patients do not realize that they are subnormal, hence many individuals of this type are overlooked unless one is on the alert. The mass surveys that have been made in this country and in others have revealed that in some localities 50 per cent or more of the inhabitants have been infected, with only a small proportion actually complaining of the subjective symptoms of the disease. Anemia is the chief characteristic, the hemoglobin being 30 per cent or less in the severe cases. The patients have a peculiar sallow, muddy complexion, differing from that of pernicious anemia or of ordinary secondary anemia. In the advanced stage we may encounter edema of the feet and legs, dyspnea, a hemic heart murmur, and at times albumin and casts in the urine, so that a mistaken diagnosis of cardiovascular disease may easily be made. The patients do not perspire so freely as do normal individuals. If the infection is acquired in childhood, as is common, growth is abnormally slow . . . the patient is "stunted," the hair development is scanty, the appearance of the secondary sexual characteristics is delayed, and in girls, as pointed out by Stiles,[4] the establishment of menstruation is retarded, and it tends to be scanty and irregular. No definite information as to possible increase in the percentage of sterility is available. Stiles in 1910, on a visit to New Orleans, called our attention to some characteristics of the hair. It is frequently of an indefinite sandy color, neither blond nor brunette, is deficient in oil, and hence of a peculiar dull, dry appearance. This, with the rather characteristic anemia, has often led me to make a tentative diagnosis on inspection alone. The blood shows the usual picture of secondary anemia, plus an eosinophilia of varying intensity. The

final diagnosis, of course, is made by the finding of the ova or the worms in the feces. Two or three examinations may be necessary, and at times special concentration methods are employed.

Naturally, many thousands of pregnant women have suffered from this complaint, yet comparatively little attention has been paid to this combination, either by obstetricians or by public health workers. It goes without saying that a condition which may so profoundly affect a woman's general health would exert its influence on her reproductive life. Lambert,[5] writing of his experience with the disease in the Fiji Islands, states that in pregnancy "the dire effects of hookworm disease are dramatized most vividly," and is of the opinion that in this region there occurs each year, from this cause, a number of deaths of mother or child, or both. Dock and Bass state that "abortion is likely to occur, and it, as well as birth at term, may be fatal in anemic patients; lactation is imperfect in hookworm patients, but improves promptly under thymol treatment; the offspring of hookworm patients are likely to be poorly developed and marantic." And again, "When hookworm patients become pregnant, the tendency to dropsy is very much increased by the disease, and in severe cases the swelling is often great. The swelling of the labia is especially troublesome as the patient approaches term."

Cinselli,[6] in 1878, reported the case of a woman dying of putrid infection after delivering a dead baby. Autopsy showed marked anemia and hookworm infestation. Cinselli thought that the uncinariasis so lowered her resistance that the puerperal infection could not be combated. Bruni,[7] in 1891, reported a patient with marked anemia due to hookworm disease (diagnosed only the day before death), who died a few weeks after the delivery of a normal child. Tridondani,[8] in 1900, reported ten cases of severe hookworm disease in pregnant women, only one of whom went to term. Six of the others spontaneously delivered prematurely, and in three instances premature labor was induced because of maternal indications; one of these three mothers died on the eighth day of the puerperium, and one on the twenty-sixth. Six of the babies were lost, one being stillborn, the others dying shortly after birth. He thought that the loss of the infants was due partly to the anemia, the hydremia, and the anoxemia, but chiefly to a toxic action of the parasites, possibly to a specific toxin elaborated by them. Pinetti,[9] in 1899, reported a case terminating in premature delivery at seven and one-half months; he felt that this outcome was due to a specific toxin, to which the patient had not had time to adjust herself, as she had been infected for only two months. He quoted Mangiagalli,[10] who reported a patient in much worse general condition who did not deliver prematurely, probably because she had had time to adapt herself to the gradually developing toxemia. Pineri's[11] patient had a severe double infection with hookworm and bothriocephalus; she delivered a living, premature baby at the seventh month. Bolli,[12] in 1907, reported the case of a woman with severe infestation and delivery at term of a child weighing 2800 gm. He found that the blood of this child was subnormal in many respects as compared to the blood of a normal newborn infant. Sacerdotti,[13] in 1909, found 38 patients with ankylostomiasis in the course of a routine study of the feces in a series of 200 pregnant women; 37 of these 38 occurred in the 152 peasant women of the series, an incidence of 24.34 per cent, showing that the disease was at that time common among the

country people of Italy; the rice growers were particularly liable to the infection. His cases were mild or moderately severe, and did not show the heavy incidence of premature interruption of pregnancy noted by Tridondani. There was spontaneous or induced abortion in three instances, six patients delivered prematurely, and in one patient it was found necessary to induce premature labor because of renal damage. Eight of these 10 patients suffered from nephritis in varying degrees (fatal in one instance), two had severe chronic bronchitis, and the majority of these 10 had developed various other debilitating conditions before or during their pregnancies. Hence he felt that the hookworm infestation was only a contributing factor, but one of considerable importance in some instances. Sinnetamby,[14] of Ceylon, in 1905, related some experiences with a series of 32 pregnant women who were seriously ill because of this complication. There were six maternal deaths, due, he felt, to cardiac failure subsequent to dilatation of the heart caused by the anemia. He stated that premature labor was the rule, but gave no details. Wilson,[15] of South Carolina, in 1918, reported three cases, two with associated toxemia; there was one fetal death on the twelfth day postpartum. Isfrán, of Paraguay, in 1926, in the course of the mass treatment of 100,000 persons, encountered 205 pregnant women who volunteered the diagnosis of pregnancy complicating their hookworm infection. He felt sure that many other such patients were also treated, in whom the pregnancies were undiagnosed. Soper[17] treated 63 women who were from two to eight months pregnant.

The incidence of renal lesions in severely infected pregnant patients is high, as noted by these various observers, and is generally thought to be due to a specific toxin elaborated by the parasites. The occurrence of eclampsia in hookworm patients has been reported by Rowan,[18] of Mississippi, Turberville,[19] of Florida, and Opocher,[20] of Italy. Rowan stated that southern Mississippi, at the time of his report (1911), was a highly infested area, and that the native white women were peculiarly subject to the toxemias of pregnancy. In 19 cases of eclampsia he could eliminate only 2 as being possibly free from hookworm disease. A number of his patients who were treated for this complication had no trouble in subsequent pregnancies. Kitrell, in discussing this paper, stated that he knew of several instances in which the combination of hookworm disease and pregnancy resulted in the death of the mother from convulsions. Turberville felt that hookworm infestation, by preparing the ground for the operation of the causative factor, had an indirect rôle in the abnormal frequency of eclampsia in his section of Florida. He encountered 7 cases in 300 pregnant women, while 2 neighboring physicians reported incidences of 6 to 200 and 15 to 350, respectively; the average ratio being estimated as about one to 500. The author felt that he had in several instances prevented the development of eclampsia by the eradication of the hookworm infection; one patient developed eclampsia before the treatment could be completed, and in another instance the combination resulted in the death of the patient. In Opocher's patient eclampsia supervened in the seventh month of the first pregnancy; labor was induced, thymol was administered, and a macerated fetus was delivered.

For several years, in a rather casual manner, I have watched for patients presenting clinical manifestations of hookworm disease in my obstetric service at the New Orleans Charity Hospital, and up to January 1 of this year I had thus detected 22 cases, each diagnosis confirmed by stool examination. Since that date, I have had a routine examination of the feces made on each patient admitted, and have thus discovered 12 infected women out of a total of 180 admitted. On one occasion there were four such patients in the ward simultaneously. All of these

patients were from the country, primarily or secondarily, the three now living in the city having come from the rural districts in the past two to five years. On this basis of a 6.7 per cent incidence, we should have had 41 cases among the 616 patients cared for by the service in 1928, instead of the seven actually detected during that year.

Many of these 34 patients had light infestations, and some might be designated as carriers, though even the carriers are somewhat subnormal, as noted by Dock and Bass. A few were severely infected, as shown chiefly by the anemia; thus, of the 19 patients on whom blood counts were made, the total red count was 3,000,000 or less, with the hemoglobin between 25 and 50 per cent in 11 instances, and in two of these it was less than 1,000,000. Nine of the 34 patients had toxemias of varying degrees of severity, and 8 of these 9 were in the above group characterized by marked anemia. In addition, one patient admitted one month after delivery with puerperal parametritis and hookworm disease gave a history of antepartum eclampsia. Of three eclamptic patients recently studied, one, from the country, was found to be heavily infected; ova of Ascaris lumbricoides were also found. The other two, one from the country and one from the city, were free from this complication. I would expect negative findings in my eclamptic patients, as these women are generally urban, because of the difficulty of transporting such patients from more or less distant points. These findings are in accord with those noted above, and it would appear that severe hookworm disease does predispose to the toxemias of pregnancy, possibly through the action of a specific toxin, but more probably because of the very poor general condition of the patient.

There were only 3 spontaneous interruptions of pregnancy in this series, probably because the majority of the patients were not severely infected. Two patients were very anemic, one had a red cell count of less than one million, with general edema; the other had a red count of 1,170,000, and was toxic, with a systolic blood pressure of 162. Both delivered at the seventh month. The other patient was the one suffering from eclampsia; she also delivered at the seventh month. These babies were stillborn. Several of the babies born at term were smaller than normal, but otherwise were apparently healthy.

As it is clear that this complication affects the pregnant woman unfavorably, and may in severe cases cause the loss of the child, it has been my policy to treat these patients along accepted lines. Thymol, 3 to 4 gm., in divided doses, preceded and followed by a purge of magnesium sulphate (not castor oil), has been used in most instances. It is important that no oily substance of any kind or alcohol in any form be taken for the first eight to ten hours after the thymol, because of the danger of absorption of the drug in these media. Dock and Bass state that thymol may produce premature labor, and hence should not be used in pregnancy, but this has not been my experience, and Dr.

Bass tells me that this statement was based mainly on theoretic considerations. Carbon tetrachloride, in 3 c.c. doses, together with 30 to 40 gm. of magnesium sulphate, was given to some patients. Soper and Isfrán used this drug in doses of 2.4 c.c. The usual treatment at present employed in hookworm eradication campaigns is a mixture of carbon tetrachloride and oil of chenopodium, the best proportions, according to E. C. Faust, Professor of Parasitology, Tulane University,[21] being 1.8 and 0.7 c.c., respectively. Lambert states that oil of chenopodium is claimed by some to be contraindicated in pregnancy, but in Isfrán's opinion this idea is erroneous. If carbon tetrachloride is used, it is highly important that it be absolutely pure. Lambert treated 42,000 persons with this drug without untoward developments, but in the next 8,000 he had three deaths, due to impurities in the preparation used. At present, in the Charity Hospital, thymol is preferred, because of the occasional occurence of toxic manifestations following the use of carbon tetrachloride. The treatment, whatever drug be used, should be repeated several times, as one treatment usually fails to remove all the parasites. It is well to check the thoroughness of the treatments by repeated stool examinations. Reinfestation is very common, hence the patient should be cautioned as to its possibility, and should be instructed as to the methods to be pursued in avoiding its occurrence.

Practically all observers agree that treatment during pregnancy does not cause abortion or premature labor. Lambert stated that he had treated hundreds of pregnant women with carbon tetrachloride with no abortions as a result. Isfrán, as well as Soper, had similar experiences. The former noted five abortions occurring from eight to twenty-nine days after treatment in the 63 cases followed up by him, but did not think that the drug was responsible for any of these interruptions. In Soper's series of 63 cases, two abortions occurred on the tenth and twelfth days, respectively, but the author did not think that these occurrences were due to the treatment. My experience has confirmed these observations, and the majority of my patients were treated so soon as the diagnosis was made, with no deleterious effect on the pregnancies. The three spontaneous interruptions of pregnancy, noted above, occurred in untreated patients, delivering shortly after admismission, before the diagnosis was made. It would appear that treatment should tend to prevent these spontaneous premature deliveries that are liable to occur in the severer cases.

It is evident, then, as recently stated by Gamble,[22] that hookworm infestation is still a public health problem in the southern states, though the surveys and mass treatments so diligently pursued have reduced the percentage of infected persons markedly. Its occurrence in conjunction with pregnancy is not at all uncommon, as is shown by the fact that, in a city hospital, I easily detected these 34 cases. There

can be little doubt that this disease predisposes to the development of toxic states in severely infected pregnant women, and that it is a potent factor in increasing the percentage of premature interruptions of pregnancy in such patients. Treatment along accepted lines is well borne, does not cause interruption of pregnancy, and is of distinct benefit to both mother and child.

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MAISON BLANCHE BUILDING.

TRICHOMONAS VAGINALIS, DONNÉ

SECOND REPORT OF EXPERIMENTAL AND CLINICAL OBSERVATIONS

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A REPORT on a six months' study of Trichomonas vaginalis was submitted to the *Journal American Medical Association* for publication in June, 1928. Today we wish to add a brief summary of the observations made since that date. The experimental work was done at Columbia Hospital with the cooperation of Miss Charlotte Colwell.

I. CLINICAL OBSERVATIONS

Routine microscopic examination of diluted fresh vaginal secretions has led to a diagnosis of Trichomonas vaginalis vaginitis in 50 private patients during an eighteen-month period. Trichomonas vaginalis has not been found in a single patient who has been entirely free from symptoms of leucorrhea or vaginitis. However, a number of women had been able to keep the condition under control by douching one or more times each day. The duration of symptoms has varied from a few days to more than seven years. Most of these patients had been previously subjected to a variety of treatments ranging from antiseptic douches to hysterectomy. One girl who had had vaginitis for seven

years gave a history of 3 vaginal operations, and shortly before my examination a hysterectomy had been advised elsewhere. Only 3 pregnant women in approximately 150 examined had Trichomonas vaginalis and 2 of these were cured during the pregnancy. The third had many parasites at the time of delivery and still has the infection as she has been unable to return for adequate treatment.

A review of the literature shows that a number of writers do not consider Trichomonas vaginalis pathogenic. This belief probably explains the indifferent attitude of most gynecologists. The rarity with which this condition has been diagnosed is due to the fact that diluted fresh vaginal secretion is not considered an essential part of a gynecologic examination. Observations made during the past eighteen months have convinced me that one should not depend on stained slides and neglect the information which is so easily obtained from the examination of fresh secretion. Furthermore, I am convinced that with few exceptions Trichomonas vaginalis rather than the associated bacteria are the cause of the very annoying vaginitis with which these parasites are associated. All acute symptoms are usually relieved within a few hours after a treatment which kills most of the trichomonas. Unless some form of treatment is continued at frequent intervals there is always a prompt recurrence of the irritating discharge and acute symptoms of vaginitis when the trichomonas increase sufficiently in number. Permanent relief has been secured in every patient whose infection with Trichomonas vaginalis has been cured. Culturally these flagellates will not show evidence of growth unless human blood serum is present in an adequate amount in the medium. Growth in the vagina appears to be most rapid during the menstrual period when an excess of blood is present. At other times they are associated in the diluted fresh secretion with large numbers of leucocytes.

The pus cells decrease rapidly and largely disappear in most cases within a short time after it is no longer possible to demonstrate trichomonas. Reappearance of the flagellates in considerable numbers is always accompanied or soon followed by large numbers of pus cells in the vaginal discharge. It is, therefore, my belief that Trichomonas vaginalis is a pathogenic flagellate and the specific cause of a most annoying and persistent vaginitis.

Thus far it has not been possible to determine the source or method of infection in a single instance. A number of histories indicate some relation to coitus and rarely trichomonas are observed in the urines of men patients at the hospital. However, I have examined the urines of many men whose wives had Trichomonas vaginalis without finding flagellates. Lewis and Carroll reported the finding of trichomonas in the pelvis of both kidneys, bladder, and vaginal secretions of a patient. Once urologists begin to look for this condition it is probable that other cases will be found. Direct implantation of Trichomonas vaginalis

appears necessary since these flagellates die so quickly under unfavorable conditions. Nevertheless I have been unable to determine the source of contact and no two cases have come from the same household. It has not been possible to test routinely the feces of these patients but trichomonas have not been found in the few examined.

Examination of vaginal secretion should be made immediately after a period or after the patient has not douched for forty-eight hours.

TREATMENT

Trichomonas vaginalis may be killed by a variety of antiseptics and various methods of treatment. In our first report the relative killing effects of various drugs were shown. They may be killed by drying, heat, and by a sufficient degree of cold. It is believed that drying and heat may be used effectively if combined with other methods of treatment. Theoretically it should be possible to eliminate Trichomonas vaginalis from the vagina with a single thorough treatment. It is frequently difficult or impossible to demonstrate a single trichomonas forty-eight hours after a thorough treatment, but following a period they may be present in great numbers although none could be found just before menstruation. It would seem that these flagellates must be harbored in inaccessible places as under the inflamed and thickened vaginal mucosa, or possibly in the cervical canal. Treatment must be continued at frequent intervals until all pus and blood have disappeared. It is also necessary to reexamine the patient immediately after the menstrual period for several months before she may be considered cured.

The following plan of treatment is now being used with some success for the group of patients who have had more than one relapse following an apparent cure. At least three times each week the vagina is thoroughly cleansed with liniment of soft soap. After the excess of soap is removed an antiseptic powder is blown onto the cervix and vaginal vault. On other days the patient uses a hot douche containing liniment of soap or compound solution of cresol. A special douche tip permits thorough distention of the vagina. Office treatments are continued during menstruation since that is the time when the relapse seems to occur. Iethyol glycerine tampons are of value during the acute stages of vaginitis, but they appear to be of little value in these chronic cases. It is believed that every case can be cured with persistent treatment although it may require many months for some.

II. EXPERIMENTAL OBSERVATIONS

After many experimental attempts to grow Trichomonas vaginalis in an artificial medium, we obtained a satisfactory growth in Locke's solution to which approximately 5 per cent of whole human blood had been added. Later it was found that a like amount of relatively fresh

human serum could be substituted for the whole blood. Dextrose broth with 5 per cent human serum appeared to be a better medium than the Locke's solution provided the P_H was similar to that of human blood. The trichomonas seemed to grow best and remain active longest in tubes containing 15 to 20 c.c. of the medium. Using this type of medium eight strains of trichomonas were successfully grown during the spring of 1928, and carried through a varying number of subcultures.

A new cultural study was started October 13, 1928, in glucose serum bouillon containing 5 per cent human blood serum. Transplants were made every two, three, or four days, usually to the same medium; occasionally switching to a Locke serum medium. The trichomonas continued to grow actively in every transplant until the night of December 21 when an accident to the mechanism of the incubator regulator caused the temperature to rise to 50° C. or higher (the thermometer registers only to 50° C. or 121°F.). Of the six subcultures of trichomonas in the incubator none were alive in the morning. Bacterial cultures subjected to the same temperature were unharmed.

Following the loss of this culture, which had been carried to the twenty-third transplant, we inoculated eight additional strains in the same type of medium but there was no growth. These specimens had been inoculated in a small amount of glucose bouillon or Locke's solution at the office and a few hours later transferred to the culture medium at the Columbia Hospital laboratory. In each case the trichomonas appeared rather inactive when inoculated and the following day had apparently disappeared.

A new culture was obtained from an untreated patient by inoculation directly into Locke's serum medium on March 15, 1929. Twenty-five days later this was killed by excessive heat in the incubator. It had been carried to the seventh transplant. More recent attempts to grow trichomonas from treated patients have been unsuccessful. A few have grown actively in the first transplant but have disappeared in the second or third.

Morphologic studies of Trichomonas vaginalis have been made by a number of observers. Among the best descriptions are those given by Lynch in 1915 and Hegner in 1925. The later study was made from smears which were fixed in Schaudinn's solution and stained with Heidenhain's iron harmatoxylin. We have not attempted a study of stained specimens, but by means of dark-field illumination we have confirmed in most respects the published descriptions. The size and shape of Trichomonas vaginalis vary markedly in different strains and at times in the same one. This is due in part to the rapidity of growth and cell division. A healthy trichomonas is somewhat pear-shaped. Four flagella arise from the anterior end of the organism as two pair, each with a common attachment. There is a tail-like protrusion at the

other end, which apparently is used as an anchor. During life the flagella appear to be in motion at all times. In dark-field studies the movements of the undulating membranes may be followed, but this is not seen in ordinary observations under lower magnification.

Trichomonas which are slowly dying in an old culture become spherical and are covered with many bacteria. It would appear from the large numbers attached to these feeble organisms that bacteria may be the cause of their death. Trichomonas which are experimentally killed slowly as by warming the culture to above 46° C. for ten minutes, also become round or slightly oval and resemble large leucocytes. If killed suddenly by glycerine or alcohol the shape is not changed.

From time to time we have observed masses of what may be dead trichomonas or some sort of cyst formation. It has not been possible to grow trichomonas in a subculture from a tube in which the active organisms disappeared and the cyst-like forms appeared.

Andrews in 1926 reported that Trichomonas hominis is killed in solutions heated to 48° C. for ten minutes. Using this as a basis for treatment Lewis and Carroll report the cure of a case of Trichomonas vaginalis vaginitis with diathermy. Believing that there might be some difference in the thermal death point of Trichomonas vaginalis and Trichomonas hominis we tried the following experiment: A small amount of an actively growing culture was placed in a small thin-walled test tube and held in a water-bath for ten minutes. At the end of this time a drop was examined under the microscope and the rest inoculated into our regular serum culture medium which had been previously warmed by placing in the incubator. Tubes were also placed in the ice box to determine the effect of cold.

THERMAL DEATH POINT OF TRICHOMONAS VAGINALIS

TEMPERATURE CENTIGRADE	TEMPERATURE FAHR.	WATER-BATH 10 MIN.	ACTIVITY IN DROP	CULTURES
42°-43°	108°	"	Very active	No cultures made
44°-45°	113°	"	Slight activity	No growth
46°-47°	115°	"	in clumps	No growth
48°	118°	"	None	No growth
9°	48°	Ice box 12 Min.	Very active	Growth active
9°	48°	Ice box 24 hr.	None	No growth
Control in incubator				Active growth

Results shown in the above table indicate that 46° C. + for ten minutes will kill Trichomonas vaginalis. It is apparent that they may also be killed by cold.

Our experimental observations show the need of an intensive study of Trichomonas vaginalis. Data on each culture must be much more

complete than in the past. So far as possible the life history of each strain must be worked out. We should record the name of the person from whom the blood serum is obtained as well as the host of the Trichomonas vaginalis strain studied.

Both experimental and clinical evidence suggest that the virility of these flagellates varies at different times and that they may be killed more easily during the late winter and early spring. In another year it may be possible to state this more definitely.

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A PRELIMINARY REPORT ON TEMPORARY ROENTGEN-RAY CASTRATION IN THE TREATMENT OF SUBACUTE ADNEXAL INFLAMMATION

By John Osborn Polak, M.D., F.A.C.S., Brooklyn, N. Y.

(From the Service of the Long Island College Hospital)

IT IS now an accepted principle that there is no operative treatment for acute salpingitis for, unless a local abscess forms in the culdesac which admits of vaginal drainage, the management of this type of infection is essentially medical. *Only the "cooled case" should be operated upon, and then operation is not done for cure of the infection, but for the relief of symptoms traceable to the resulting pathology.* Rest and time usually effect a symptomatic cure. In support of this statement Holtz reports that in more than 1000 cases of acute salpingitis treated by purely expectant methods, a clinical cure was recorded in 82 per cent, while 12 per cent had functional cures with resulting conception (in only 2 per cent was there absolute failure) and such results are being duplicated in almost every clinic.

In a study of the case histories of patients with this disease, admitted to our clinic in the past five years, fully 70 per cent may be classed as gonorrheal. These women gave a history of recent marriage or illicit coitus followed by skenitis, bartholinitis, or endocervicitis. This is a larger percentage than has been credited to Neisserean infection by most observers. Eighteen to 20 per cent were traced to a nonspecific origin, pelvic lesions following postabortal or puerperal infection; while 5 to 7 per cent were tuberculous. This ratio of incidence cannot be checked up by bacteriologic findings, for many women who marry men suffering from a chronic gleet contract an infection

but pass through such a mild type of cervical and urethral inflammation that the profuse discharge loaded with gonococci is absent at the time that they present themselves for treatment.

Whether the infection is of specific or nonspecific origin, the pathology is much the same, i.e., an extension of the inflammation from the endometrium to the endosalpinx, always bilateral, though the severity of the infection and the tissue reactions may be greater on one side than on the other. Formerly it was taught that in gonorrheal infection the extension was always bilateral, while in septic cases following operation, abortion, or childbirth, the invasion was through the parametrium and usually only one tube was involved. Repeated autopsy studies with serial sections of the uterus and tubes have shown that any infection which extends from the endometrium involves the endosalpinx of both tubes. Likewise, all tubal infections tend to subside spontaneously. The gonococcus cannot exist without oxygen and once it has been encapsulated by tissue reaction, its death is inevitable and activity ceases. The recession of bacterial activity and the evidences of clinical improvement are always coincident.

Curtis states that gonorrheal salpingitis is a self-limited process and that the exacerbations are in reality fresh infections either from operative extensions from an infected lower genital tract, such as an infected cervix, or from the male. To this, we can in part subscribe, for in our experience pelvic and sexual rest in time always effect a symptomatic cure; this, however, may be expedited by temporary castration producing a suspension of the periodic menstrual engorgement. The exacerbations in temperature and leucocytosis occur at the menstrual period and are explained by the fact that the cervix is open during menstruation and the protecting mucus is washed away by the menstrual flux, while the menstrual blood and clots act as excellent culture media. Skene's tubules often remain as infective foci and should always be destroyed. The gonococcus does not live long in the lumen of the tube, though it has been assumed that the bacteria remain viable in the deeper structures of the tubal wall. This last impression has been disproved by Curtis, for his study of over 200 thoroughly ground fallopian tubes reveals the fact that it is almost never possible to obtain the gonococcus (by culture) longer than two weeks after the disappearance of fever and leucocytosis. This observation coincides with the clinical picture of this form of infection—and were it not for coitus and the recurrence of menstruation, absorption of the products of tissue reaction would go on rapidly. The effects of sexual trauma must not be underrated, for clinical experience has shown that most careful bimanual examination will break down barriers and excite cellular activity in the "uncooled" case; hence, coitus must have a similar effect.

When the organisms are nonspecific, more or less of a similar condition exists. The acute attack tends to subside, and the exudate is absorbed in the same way as though a specific organism were present. The difference, however, is in the fact that nonspecific organisms may be anaerobic. This permits the inflammatory reactive processes to quiet down, but the retained organisms may retain their virulence and have a decided potentiality for harm.

The life of the buried streptococcus has never been definitely settled, for it has been isolated from the tube as late as ten, twelve, and nineteen years from the original attack. This makes operation always more hazardous when there is a history of septic infection. In both types of infection autosterilization occurs, and the woman recovers by developing her own immunity which protects her against the bacterial invasion that has taken place. The only difference is that the organisms in specific infections have a limited life history, while those of nonspecific infections retain their activity for an unknown period of time. The cardinal principle of treatment is rest in bed for days or weeks. Pain is relieved by codein and aspirin, the therapeutic light, or the ice bag, whichever gives most comfort to the patient. The lower bowel and pelvic colon are kept empty by small enemas. Body resistance and elimination are maintained by small repeated blood transfusions, hypodermoclysis, and intravenous infusions of glucose while tissue reaction is stimulated by protein injections and vaccines. Menstruation and the resumption of marital relations frequently relight a quiescent process, for pelvic and sexual rest are the basic factors in treatment. We operate for the results of infection; when, therefore, should operation be done?—how long should it be delayed?

In 1908, F. F. Simpson presented before this Society his results in the conservative treatment of 400 cases of acute adnexal infections. At that time he laid down the principle that no patient should be operated upon until the temperature has been normal night and morning for a period of at least two weeks; that the leucocyte count must be below and remain below 11,000; that the "poly" count must be 75 per cent or less, and that pelvic manipulation, as bimanual examination, should not cause a rise in the temperature or in the leucocyte or "poly" count. To these requirements we have added that the exudate must be hard and insensitive and show evidence of being absorbed; and that the blood sedimentation time must be ninety minutes or more. These conditions, when they obtain, prognosticate a good surgical recovery and allow conservative operations which permit the retention of the menstrual function. Experience has taught us that there is no exception to these minimum requirements. All of this takes time and as Miller so aptly puts it, "the wise surgeon is the one who waits and continues to wait until the patient by her immunity has overcome the infection."

Rest in bed, the therapeutic light, the ultraviolet ray, diathermy, hot vaginal douches and vaginal packs have all been credited with aiding the organization and absorption of pelvic exudates, but the greatest of all is time. The recurrence of menstruation always activates the process, causes a slight rise in temperature, produces an increase in the leucocyte count and increases the pain. Clinically we have noted in those cases of severe puerperal infection which are followed by prolonged amenorrhea that the pelvic exudate and the pelvic symptoms rapidly disappear. In line with this observation, in 1918, Dr. Beck and I operated upon a woman on a mistaken diagnosis and found the pelvis "too hot"; the adhesions were diffuse and injected, the tissues friable and edematous, and before going far with the procedure, we decided that, because of her youth, it would be better to close the incision than to remove her entire pelvic structures. This we did and because of a persistent metrorrhagia we subjected her pelvis to x-ray treatment. Nonsterilizing doses were used, but sufficient dosage was given to produce an amenorrhea which lasted for several months. The surprising thing about this case, was, that the exudate simply melted away, no further exacerbations ever occurred and the patient was clinically cured. Similar cases were treated in 1920 and 1921, but the real significance of this treatment was not brought to our attention until 1924 when Naujoks published his article on temporary sterilization in women suffering from pulmonary tuberculosis, and in 1926 when Gutman and Bott published their thesis suggesting temporary sterilization in the cure of adnexitis and parametritis. During the past five years we have treated 34 patients on these principles, i.e., producing a temporary x-ray castration after the first acute symptoms of tubal inflammation subsided. In this small series there were 16 cases of gonorrheal origin; 10 giving histories of previous abortion or labor, belonging to the puerperal class, and 8 which fell in the tuberculous group. The periods of amenorrhea ranged from four months to one year; in all the patients the pathologic exudate in the pelvis rapidly disappeared, the uterus became mobile, and the actual adnexal masses were easily defined. It is surprising when operating upon these women—and incidentally but few have needed operation—to find how free the pelvis is of adhesions and how easily existing ones are separated. Of the seven women operated upon, all had retrodisplacements with adnexa in the culdesac. The other twenty-seven had the uterus forward and have had complete symptomatic cures. In no case has menstruation failed to reappear, and one woman has become pregnant.

It will be argued that the same results can be secured by rest and time. To this I do not subscribe, for premenstrual, pelvic and abdominal soreness have been a more or less constant story in conservatively cured cases. This symptom has occurred right up to the time of the menopause when apparently all of the subjective symptoms seem

to disappear. On the other hand, in the cases treated by x-ray the premenstrual and peritoneal soreness was absent. The value of x-ray sterilization to our armamentarium has been best demonstrated in patients with tuberculous salpingitis, peritoneal extension, and persistent temperature. These patients show temperature reactions at each succeeding menstrual period. Furthermore, these patients usually have a leucopenia and a low sedimentation time—both evidences of poor resistance. Temporary x-ray sterilization has changed the picture in these women and has allowed hygienic and dietetic measures to do their work without handicap. We append a detailed technic for the roentgenologist and suggest that the best time to give this treatment is just prior to ovulation, for at this time the more mature follicles can be destroyed without injuring the primordial follicle. Very small dosage should be employed; this may be repeated if necessary at subsequent treatments.

While our series is too small to draw any definite conclusions, I believe that by the employment of this simple means of treatment we can shorten the convalescence period in tubal infections, conserve the adnexal function, and save many women from mutilating operations.

ILLUSTRATIVE CASE HISTORIES

I have selected four cases which I believe are so typical that they will prove my point. Skene's glands should be destroyed as a preliminary in all gonorrheal cases.

CASE 1.—Mrs. B., twenty-four years old, married two months, noticed burning urination and profuse purulent vaginal discharge while on her wedding trip. She was in bed all of the week following the menstrual period, complaining of severe lower abdominal pain and fever. On entering the hospital, two weeks after marriage, she presented the clinical picture and signs of an acute gonorrheal infection of Skene's glands, cervix, uterus, and both tubes. She was put to bed and treated expectantly. In fifteen days her temperature was normal, the discharge was mucopurulent, and well-defined masses could be outlined on both sides of the uterus. She was treated with the therapeutic light, milk injections, and the violet ray. All of her symptoms tended to improve, only to light up with the occurrence of menstruation. Furthermore, these symptoms recurred at the succeeding period, notwithstanding the fact that she had not resumed her sexual life. After the second exacerbation she received two x-ray treatments which checked her menses for four months. Absorption continued and the pelvis was free from any demonstrable pathologic condition. Early in 1927, she divorced her former husband and married again. Considering herself perfectly well, she wished to become pregnant. Insufflation demonstrated her tubes to be closed. She was operated upon and, the fimbria and adhesions were freed on one side, while the opposite tube which showed nodular obstruction was removed. Her complete relief from premenstrual pain and abdominal soreness was marked.

CASE 2.—Mrs. D., aged twenty-one, married, became pregnant and contracted specific infection at the same time. As her husband did not want children, she had an abortion performed at the sixth or seventh week. She was very ill on admission to the hospital; temperature 104° F.; pulse 130; marked abdominal

distention and tenderness, with a diffuse mass running from pelvic wall to pelvic wall. She was treated with rest, milk injections, and light therapy. In about ten days' time her temperature began to subside. When the menses recurred, all symptoms became exaggerated. Two x-ray treatments were given which were followed by an amenorrhea for six months with complete subsidence of pelvic lesions. This woman was examined and her pelvis found to be free from exudate; left ovary was cystic, the size of a hen's egg, and insensitive. Patient had no complaints.

CASE 3.—Mrs. Z., aged thirty, married and sterile. Examination of husband was negative. She complained of pre- and co-menstrual dysmenorrhea, leucorrhea, and menorrhagia. Examination showed a mild endocervicitis with a halo of erosion about the external os, and a retroflexed uterus with tuboovarian masses in both fornices. She ran an evening temperature of 100.4° F.; had a low leucocyte count and a sedimentation time of only forty-five minutes. The lungs were x-rayed and a pulmonary lesion was ruled out. After observation for a week, at the request of her husband who was a physician, we operated and found tubal tuberculosis with peritoneal extension; there was no free fluid, but miliary tubercles were scattered over both broad ligaments, sigmoid, and peritoneal covering of uterus. Both tubes and the cornua of the uterus were removed. Convalescence was uneventful until her menstrual period when she had temperature, peritoneal pain, tension and rebound. This was repeated at her next period. It was difficult to persuade her husband to allow temporary castration, but finally he consented. She was given two x-ray treatments just after her menses. There was an amenorrhea of eight months during which time her general condition improved, she gained weight, and her pelvic symptoms entirely subsided. On bimanual examination the uterus was found to be small and movable; the ovaries were free and palpable, and vaginal discharge had ceased. When seen in March of this year, menstruation was regular without pain and she considered herself cured.

CASE 4.—Mrs. F., aged twenty-one, married, was operated upon in February, 1927 in Newark for what was diagnosed as appendicitis. The appendix was removed and the ileum was found adherent in the pelvis; adhesions were freed with considerable bleeding so that the surgeon desisted from further exploration. The wound healed, but the temperature and pain in right side and pelvis continued. After consultation a vaginal incision was made in the right broad ligament. The convalescence was slow and attended with continuous evening temperature, loss of weight, distention, and periodic vomiting spells preceded by colic. This continued until she entered our service in November, 1928. At this time she weighed 90 pounds, was pale and pinched looking. She had an evening temperature of 102° to 103° F., and pulse 120 to 140; the abdomen was distended, and there was general tension but no rebound except in the left lower quadrant. Each day she vomited after an attack of intestinal colic, though enemas and Harris enteroclysis caused the free passage of gas. Pelvic examination showed a small uterus pushed forward and to the right by a mass in the left lower quadrant which involved the ovary, tube, and sigmoid. The attacks of pain and reversed peristalsis began in the left lower quadrant. She was transfused and treated with daily glucose infusions, the therapeutic light, and violet ray. For two weeks in each month the temperature was lower and her intestinal symptoms better, only to be activated for a week before and during each period. Gradually a large fluid accumulation formed in the culdesac. This was incised, evacuating a quart of serum containing tubercle bacilli. There was some local relief but no general improvement. I then persuaded her family to allow me to stop her menstruation with very mild repeated doses of x-ray. There was a gradual but complete cessation of symptoms. The exudate was absorbed, the temperature fell, and all of her intestinal symptoms disappeared.

From time to time her improvement has been continuous. When last seen in March, 1928, she had gained twenty pounds and her pelvis was free from any palpable pathologic condition.

My associate, Dr. A. L. L. Bell of our X-ray Department, has kindly supplied me with details of roentgen treatment in subacute pelvic infections with or without menstrual disturbances.

The dosage must of necessity vary in different cases owing to the variation in the distance of the ovaries from the anterior abdominal wall, and also to their distance from the skin surface posteriorly. The object of the treatment is to apply to the ovaries an x-ray dose of about 215 to 230 electro-static R-units (Duane-Glasser), using 180 to 185 K.V. and a filtration of 0.5 cm. of Cu and 1 mm. of Al. The ovaries are assumed to be 0.4 of the total depth of the pelvis from the anterior skin surface. In a patient whose total pelvic depth is 25 cm., the ovaries are calculated to be 10 cm. from the anterior skin surface and 15 cm. from the posterior surface. Using a depth dose chart, we find that at a depth of 10 cm. 35 per cent of the dose administered to the skin reaches the ovaries, and at a depth of 15 cm. between 32 and 35 per cent of the dose administered to the skin reaches the ovaries. Therefore, in treating such a patient, an area 20 cm. square anteriorly and posteriorly is given a dose of 320 R-units. The sum of the 35 and 33 per cent depth doses gives 217.6 R-units applied to the ovaries. These doses may be given at one time, but we usually administer them on successive days; there are no reactions from doses of this size, but we think it safer to divide them. In some cases where the infection is particularly active we have divided the treatments, so that only about 50 R-units (depth dose) are applied at one time. This dose is not repeated for at least two months, or until after the second menstruation following the first treatment. With these doses we have not produced any permanent amenorrheas.

20 LIVINGSTON STREET.

ACUTE PUERPERAL INVERSION OF THE UTERUS

By Palmer Findley, M.D., Omaha, Neb.

FOUR papers have appeared in the Transactions of the American Gynecological Society on this subject. W. H. Byford, in 1879, reported a case of chronic inversion; Edward P. Davis, in 1893, reported a single case of acute inversion; B. Bernard Browne, of Baltimore, in 1899, reviewed operative procedures; and Reuben Peterson, in 1907, discussed anterior colpohysterotomy in the management of chronic inversion.

Browne expressed the opinion that inversion of the uterus was probably more frequent in ancient times as judged from frequent references and accurate descriptions contained in the writings of Hippocrates, Aractius of Cappadocia, A. D. 30-60, Celsus, A. D. 1-50, Themison, B. C. 50, Rhazes of the eleventh century, and Ambrose Paré in the middle of the sixteenth century. That inversion of the uterus may well have been of more frequent occurrence then than now is supported by the methods then employed in delivery in the standing or kneeling position or in sitting upon a hollow stool. A more potent factor than that of position was the lack of means of expediting labor to prevent spasmodic exhaustion.

In 1847 Valentine de Vitry reduced an inverted uterus of sixteen months duration and from that time on we find numerous procedures devised for the correction of the lesion.

All writers on the subject refer to the extreme rarity of inversion. From the fact that the accident occurs more often in homes and in the hands of the incompetent, rather than in hospitals under skilled management, it is fair to assume that inversion is not so rare an occurrence as recorded statistics would indicate. As evidence of this assertion W. H. Fisher collected 38 unreported cases in the neighborhood of Toledo, Ohio, and adds that he was unable to make a complete survey.

I have seen four acute puerperal inversions of the uterus. The first was in a European clinic. A version and extraction had been performed; the placenta was delivered by forcible expression under general anesthesia when the uterus completely inverted. There was much loss of blood and extreme shock. An ineffectual attempt was made at reduction; this was followed without delay by a vaginal amputation. Two hours later a postmortem examination revealed the transfixion of a loop of bowel by sutures. Death was the probable result of shock from operation, superimposed upon the initial shock of the inversion.

Following is a brief history of three cases seen in consultation:

Case 1.—Mrs. A., aged twenty-four years, primipara, was delivered by forceps of a full-term baby weighing 8 pounds. Failing to deliver the placenta by ex-

pression, the hand was introduced into the vagina. It was then that the inverted fundus was discovered. The placenta was removed and the vagina packed with gauze, but the hemorrhage was not effectually controlled. All means at hand were employed to resuscitate the mother, and help was summoned. I saw the patient some six hours later; she was in extreme shock and blood was oozing through the vaginal pack. We removed the pack and an ineffectual effort was made to reduce the inversion. A pack was again inserted, but this also failed fully to control the bleeding. With the able assistance of two surgical nurses and two doctors the fundus was amputated. A minimum of ether was employed; the operation consumed not more than ten minutes. This case occurred in a farmhouse where there were no facilities for blood transfusion. The patient died within a few hours.

CASE 2.—Mrs. B., aged twenty-seven years, primipara, delivered herself after a prolonged labor. The attending physician found difficulty in delivering the placenta and doubtless used considerable force upon a relaxed uterus. Following closely upon the expression of the placenta, there was profuse bleeding and shock, but this condition did not last long. The attending physician failed in his efforts to reduce the inversion. Twelve days later I was called to operate upon the patient. The inverted fundus, which was fully delivered from the vagina, was partially gangrenous. The fundus was amputated; recovery followed. The operation was performed on a kitchen table in a farmhouse.

CASE 3.—Mrs. C., aged thirty-five, para iii, was delivered by low forceps after a fairly easy labor of six hours duration. The placenta was expressed, but no great amount of force was employed. The inverted fundus appeared at the vulvar outlet immediately following the delivery of the placenta. There was little loss of blood and no pain. The patient went into profound shock but had rallied somewhat when I saw her an hour later. Efforts at reduction failed, due to the presence of a gripping cervix. The patient's pulse was running at about 160, but disappeared at every effort toward reduction. The fundus was pushed back into the vagina, a gauze pack applied and for four hours efforts were directed toward restoring the patient, but there was little or no improvement. Another effort was made to reduce the displacement and we again failed. I then proceeded to amputate the uterus. Because of the extreme shock I was able to complete the procedure without general or local anesthesia and without occasioning pain to the patient who was in a semiconscious condition. To those who advocate abdominal section in all such cases I would say it is my belief that this patient could not have withstood the added shock of the operation. As it was, the pulse regained its force immediately upon removal of the uterus and recovery was speedy and complete.

In perusing the literature on inversion of the uterus one is impressed with the diversity of opinion relative to its frequency of occurrence, its etiology, mechanism, prognosis, and treatment. In 1,932,164 labors collected from the literature, there were 17 inversions, or one to 113,068 labors. Zangemeister estimates 1 in 400,000, while Küster's estimate is 1 in 23,000. The extreme rarity of the occurrence is evidenced by the finding of but 76 cases reported in German literature in the past twenty-one years.

The inverted uterus has been tersely described as "upside down and inside out." Faulty technic in delivery is responsible for a large proportion of all recorded cases. Forcible expression of the placenta and traction on the cord are, of course, contributing factors in the production of inversion, but no amount of force in the effort to deliver

the placenta would invert a firmly contracted uterus, nor would the cord withstand sufficient traction to invaginate a uterus well contracted. Furthermore, these factors do not explain the occurrence of inversion in which the placenta has been delivered with no assistance. More than half the cases occur in primipara in whom fundal attachment of the placenta is more common than in multipara and the uterine contractions are more forceful. That fundal attachment of the placenta is not essential is evidenced by the occurrence of inversion in placenta previa. Moreover, a firmly contracted fundus may find its way through a dilated and relaxed lower uterine segment and cervix; hence, it is apparent that complete relaxation of the uterus is not essential to the development of inversion. Given a limited area of atony under direct pressure from above or traction from below and the contractions of the uterus may well participate in effecting a complete inversion. Reeve is quoted as saying that "the accident may occur independently of anything done or omitted."

Jones gives the following terse description of the mechanism of puerperal inversion: "After any portion of the uterus becomes indented to a considerable extent the rest of the organ seizes this invaginated portion as it would grasp a foreign body, and in attempting to expel it, turns itself inside out." This would seem to tell the story as well as it can be told. Doubtless spontaneous readjustment of a partial inversion not infrequently takes place and is seldom recognized where there is but an incupping of the fundus. Where there is general relaxation of the fundus the inverted portion is dragged in a downward direction. It is this traction in a downward direction that plays the chief rôle in forcing the inverted fundus into and through the relaxed cervical canal. The brutal force that is often applied to the uterus in endeavoring to deliver the placenta in the presence of uterine inertia and without causing inversion, adds emphasis to the factor of traction on the part of the incupping fundus. Probably one-third of all puerperal inversions arise spontaneously in the absence of traction on the cord or pressure from above. Eighteen of the 61 cases reported by Evans were spontaneous and without forcible expression or traction on the cord. Of the 437 postpartum inversions recorded by Thorn, 54 per cent were spontaneous and were not contributed to by traction on the cord or by forcible expression of the placenta.

While inversion usually occurs within an hour after labor, it has been known to be delayed until the fifth day of the puerperium. It seems incredible that a diagnosis should be long delayed, but Peterson's case eluded recognition for twelve years and Reeve's for twenty-five years. As to time of recognition of the inversion Jones, in his analysis of 191 cases of acute inversion, found 19 recognized at the end of the second stage; 44 at the completion of the third stage; and 141 within twelve hours following delivery of the placenta. It is surprising, however, to

note the great number that have escaped recognition for one or more years. Instances of mistaken identity are recorded.

E. H. Smith (1897) writes of a midwife who pulled upon the inverted uterus for three-quarters of an hour and finally completed a manual hysterectomy with one tube and ovary thrown in for good measure. Incidentally, the patient survived. But the results were not so fortunate in a case attended by a midwife who mistook the inverted fundus for the head of a second child. She completed her task, but the patient died.

McCullagh says that half the cases show no immediate symptoms. With the placenta in situ or the cervix tightly constricting the protruding uterus, there will be little loss of blood. Shock may be present without hemorrhage and is variously ascribed to the sudden decrease in intraabdominal pressure, to compression of the ovaries (McCullagh), and to traction and stretching of peritoneal structures. With shock and hemorrhage averted there may be an interval of relative safety to be followed by gangrene of the uterus from strangulation and consequent sepsis.

The mortality is variously estimated at from 14 to 25 per cent. Here, again, we are at a loss to make any reliable statement, for the reason that many of these cases occur in the home, are often unrecognized, and are seldom recorded. Half the deaths occur in the hour following delivery and possibly nine deaths in ten occur within two hours of the completion of labor. Mason and Rueker, in an analysis of 63 cases, found no mortality in hospital cases where prompt and efficient treatment was available, this in comparison with a mortality of 12.5 per cent in the hands of the doctor in the home and of 26 per cent in the group delivered by midwives. Jasche estimates that about one-fourth of the deaths result from hemorrhage, one-fourth from shock, and the remaining half from sepsis. He believes that correct therapy could reduce the mortality to 3 or 4 per cent. In the 399 cases of acute puerperal inversion reported by Thorn, the mortality was 16 per cent. Approximately half the deaths were due to hemorrhage, nearly one-fourth to shock, and a trifle over one-fourth to sepsis. Two of the patients died of pulmonary embolism.

In considering the management of acute puerperal inversion we should bear in mind that a successful correction of the inversion at the expense of a life is not an obstetric triumph. In perusing the records of cases reported in the past twenty years, I am profoundly impressed by the appalling number of deaths following early or late upon a reduction of the displacement by taxis. Phillips records a mortality of 30 per cent following reposition in the presence of shock and hemorrhage, as contrasted with a mortality of only 5 per cent where no attempt at replacement was made prior to restoration of the patient from the effects of shock and hemorrhage. To attempt reposition in the presence of shock and profound anemia is to invite disaster. Unquestionably, the sheet anchor in the presence of shock and hemorrhage is blood transfusion. In studying case reports one is impressed by the number of lives saved by the simple process of checking hemorrhage by packs and

the transfusion of blood before resorting to any methods of replacement. Such precautionary measures will lower the mortality fully 50 per cent. The uterus has been replaced by taxis and the patient succumbs to shock and attending hemorrhage. Operative procedures, both vaginal and abdominal, have been employed in the presence of profound shock and the patient died. The uterus has been replaced by taxis or operation with delayed death from sepsis. In many instances the fatalities are unquestionably the result of ill-advised intervention in the presence of shock. A blanched patient is always a poor surgical risk and here, as in placenta previa, it is imperative first to control the loss of blood, second to combat shock, and with this accomplished, it is time enough to correct the inversion. In the absence of profound shock, great loss of blood and known sepsis, the uterus should be replaced and at the earliest possible time. Under such favorable conditions early replacement is seldom difficult. Delay of one or more hours may result in a tightening of the constricting cervix and defeat all attempts at replacement short of operation.

While hemorrhage is the cause of death in the greatest number of recorded cases, sepsis following replacement must be reckoned with. About one-third of all fatalities are ascribed to sepsis. Every inverted uterus is a potentially infected uterus, and in the presence of extreme depression and acute anemia it is not surprising that the morbidity and mortality from sepsis following replacement are so great. I am convinced that results would be bettered by a more general application of vaginal hysterectomy where there is good reason to fear sepsis. I would go one step further in advocating vaginal hysterectomy where vaginal replacement has failed, rather than to enter the abdomen under general anesthesia in the presence of profound shock. Better to sacrifice the uterus than the patient. I am aware of the splendid results recorded by Huntington, Kellogg, and Irving in which abdominal replacement was effected and in the presence of profound shock, but I affirm that such an undertaking would not be justified in the hands of less skillful operators. In a personal communication from Foster Kellogg he expresses preference for abdominal reposition in the presence of shock because of the readiness with which the uterus can be replaced with almost instantaneous disappearance of shock. He is of the opinion that more loss of blood and greater intensity of shock will result from efforts at vaginal replacement. I grant that his position is defensible under the favorable conditions of master surgery and modern hospital facilities. But, unhappily, such are not the usual conditions. The dictum in force when "Knighthood was in Flower" applies here with added force, "Choose your weapon according to your cunning."

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CANCER OF THE CERVIX COMPLICATING PREGNANCY

By John A. McGlinn, M.D., Philadelphia, Pa.

THE literature on cancer of the cervix complicating pregnancy is most voluminous.

B. P. Watson, 1918, reviewed the subject and reported a most unusual case, the paper being discussed by H. M. Vineberg. This, and the recent report of E. Schumann, 1927, on the coexistence of cancer of the fundus of the uterus and pregnancy, are the only references to be found in the transactions of this Society. The importance of this subject and the paucity of our discussions justifies its consideration at this time. The subject is particularly important for the reason that the best and most modern treatment for cancer of the cervix may, in the light of more extended experiences, be contraindicated when pregnancy complicates the cancer.

It is difficult to estimate the statistical frequency of the association of cancer of the cervix and pregnancy. B. C. Hirst, 1923, reported a large series of cases showing an incidence of one case in every 12,484 pregnancies. Lately E. O. Gross reviewed practically the same number of pregnancies and found the incidence to be one in every 1,538. According to Mundell, Mussey reported an incidence of one in 437 pregnancies. Individual experiences differ just as widely. Herbert Spencer in the Lettsomian Lectures (*Proceedings of the Medical Society of London*, 1920), reports 10 cases. Hauch reports 4 cases, Gross 34, Korg 7, Bainbridge 2, myself 2, etc. Gross believes that the condition is five times more frequent than is supposed. This is most likely true if the cases of cancer which are recognized within a year after the termination of a pregnancy are included.

There is likely no causal relationship between pregnancy and cancer of the cervix in so far as their occurrence at the same time is concerned. As is to be expected the association is more likely to be found in multipara rather than primipara and in the late thirties rather than in the early twenties, these findings being dependent on the repeated traumatisms to the cervix in multipara and the age incidence of cancer in general.

J. T. Williams in an exhaustive study of the literature was only able to find records of 8 cases of the association of cancer and pregnancy in primipara. Schilling in a study of 43 cases found the average number of pregnancies in each case to be 6.9. The two cases to be reported were both primiparas, one twenty-eight years old and the other thirty-one years old.

Goodal in a very important paper read before the Philadelphia County Medical Society several years ago, advocated the cleaning up of all erosions and infection of the cervix after labor as a preventive of infections in subsequent labors. If this advice was generally followed it would mean not only a lower incidence of infections but also a lower incidence of cancer in subsequent pregnancies. The broad application of the principles enunciated by Goodal would have a beneficent effect on the health of the child-bearing woman.

Gross in 1922 reported 34 cases of cancer of the cervix occurring within a year following pregnancy at term or abortion. He urges that a close follow-up should be kept for at least a year in all women over thirty who have had either a confinement or abortion. It is our practice to observe this rule in all such cases irrespective of the age and not to discharge an obstetric patient until the cervix is in a healthy condition. The general acceptance of this rule would result, not only in the early detection of some cases of cancer of the cervix, but would prevent the development of cancer in many.

There is to be found in the literature a decided difference of opinion as to the question of the antecedence of the cancer or the pregnancy. There may be room for an academic discussion of the pros and cons of this question but clinically there can be no difference of opinion. In many cases the cancer antedates the pregnancy, and in many cases the pregnancy antedates the cancer. This is demonstrated in my two cases. Cohnstein and Gross found that cancer antedated the pregnancy in 17 per cent of the cases they studied, whereas J. T. Williams, Blumreich, Keyes and others believed that in the majority of cases the woman had cancer before she became pregnant. As a matter of fact there is no reason why a woman with early cancer of the cervix should not become pregnant nor is there any known reason why the pregnant woman should not develop cancer.

The same difference of opinion is found in regard to the question of the influence of the pregnancy on the cancer. The opinions expressed as a rule depend on what the author has observed in his individual case. If there has been rapid spread of the disease he usually argues that pregnancy has been the cause of the rapid increase. If, on the other hand, there has been retardation of the growth, specious arguments are brought forward to prove that pregnancy has a deterrent effect on the cancer. Undoubtedly many observers have noted a marked rapidity of cancer growth associated with pregnancy, such as the classical examples of Zweifel and Simpson. On the other hand, many observers, notably Weibel, Wolf, Meyer, etc., have observed a retardation of the growth, and have advanced theories in support of this observation. We recognize, however, that cancers vary greatly in their malignancy; so that, unless it is known what type of cancer we are dealing with in each individual case, it is impossible to draw any accurate conclusion on this question.

Much has been written on the symptomatology and diagnosis of the association of pregnancy and cancer of the cervix. Certain facts stand out: Bleeding is the leading symptom and a careful examination for the cause of all bleedings in pregnancy discloses the true condition. The mistake is made of considering all bleedings in the early months of pregnancy as due to threatened abortion and refraining from making an examination. In the later months of pregnancy placenta previa or accidental hemorrhage is suspected and again we fear the danger of an examination. We have become obsessed with the fear of mak-

ing a vaginal examination in pregnancy. The dangers of vaginal examination are grossly exaggerated. If we can teach how to learn something from a rectal examination, we can teach how to make a vaginal examination without endangering the patient. Unless all cases of bleeding during pregnancy and early puerperium are fully and competently examined, many cases of early cancer will be missed. There is no mystery in making a diagnosis, it is simply a case of looking for it.

I have observed two cases, one in early pregnancy properly diagnosed, and one in late pregnancy, mistakenly diagnosed.

CASE 1 was in a primipara thirty-one years old, married two years. Five months prior (June) to consulting us, she had a slight discharge and consulted a physician on account of the discharge and sterility. He found a slight abrasion of the cervix which was treated locally. She menstruated in June, July, and August. In September slight bleeding but not a regular period, no bleeding in October. Early in November she started to spot. Examination on November twenty-first revealed a uterus the size of a three months' pregnancy with a punched-out ulcer one-half inch in diameter on the posterior lip of the cervix. Dark-field examination and Wassermann negative for syphilis. Excision of the ulcer followed by extensive cauterization of the operative area was the next step in the study of the case. The pathologic diagnosis was cancer of the cervix. This was a very early case, in fact, the earliest case of cancer of the cervix I have ever seen. Complete hysterectomy was advised and refused. Radium was then suggested but the patient refused to have anything done which would jeopardize the life of the child in any way. This attitude was dependent entirely on an inordinate desire for a child. She finally consented to the use of radium, and was given 2400 mg., hours by capsule and needles into the cervix. This was quickly followed by a most remarkable disappearance of all local evidence of the disease. The uterus, however, did not enlarge and four weeks after the application of the radium she aborted a three months' fetus.

The laboratory report follows: Specimen is a male fetus, placenta and membranes. Fetus is slightly macerated: measures 17 cm. from crown to sole, 10 cm. from crown to rump, weighs 85 gm. Cord is 16 cm. long by 0.6 cm. thick. Placenta is 8 cm. in diameter by 2 cm. thick and is complete. Membranes seem slightly thickened. Placental tissue is pinkish grey in color, mottled along the border by brownish-red. Sections of placental tissue reveal slight cellular degeneration with a scattered mixed leucocytic exudate throughout. Otherwise negative. Blood vessels of cord also show this infiltrate in all layers. There is no definite thrombotic occlusion to be expected from the macroscopic appearances, but interference with vascularity has undoubtedly produced death of fetus.

Patient was discharged from the hospital in good condition with no evidence of the disease. She was examined at regular intervals and remained symptom free until the following August, nine months after the radium and eight months subsequent to the abortion. She then complained of pain in the pelvis and examination showed a small mass in the left broad ligament. Section revealed multiple metastases in the pelvis. She later developed acute mania and had to be removed to a psychopathic hospital, where she died.

This case presents some interesting phases. First, the cancer undoubtedly antedated the pregnancy in a fairly young primipara. Secondly, cauterization and radium apparently cured the cancer of the

cervix, yet pelvic metastases occurred later without any return of the local condition. Thirdly, radium, by its action on the circulation of the cord and placenta caused the death of the fetus.

CASE 2.—Primipara, twenty-eight years old. Late in pregnancy she developed severe bleeding which was diagnosed as due to placenta previa. A living child was delivered by cesarean section. She was still having vaginal bleeding when she was discharged from the hospital. I saw her soon after this and found an advanced inoperable cancer of the cervix and vagina. We gave her an application of 3600 mg. hours of radium with excellent local results and referred her to Dr. G. E. Pfahler for deep x-ray treatments. Ten months later she was in good general health but with a pelvis blocked by cancer. She is still living, one and a half years after being treated.

The interesting phase in this case is the mistaken diagnosis of placenta previa. This case, from the extent of the disease when we first saw her, must have had symptoms long before she was operated upon. Had examinations been made, the disease might have been recognized in time to have cured her cancer.

The prognosis for the mother, no matter the stage of pregnancy, is bad but not altogether hopeless. A number of reports of cures after hysterectomy, radium and cautery amputation of the cervix, are to be found in the literature. None are more interesting than those reported by Herbert Spencer. Three of his cases remained well after nineteen, twenty-two, and twenty-five years. The last of these had a child subsequently to the cautery amputation, delivered by cesarean section, who served as a soldier in the Great War.

The prognosis for the child depends on the stage of pregnancy and the method of treatment adopted. Obviously the child's chances are best when the cancer develops late in pregnancy and when delivery is made by cesarean section without any prior treatment of the cancer. Per contra, the prognosis is worse when the cancer occurs early in pregnancy and the uterus is removed. The effect of treatment on prognosis of the child will be discussed later.

Next to the early recognition of the disease, the question of treatment is most important. All authorities are in accord that abortion has no place in the treatment of this complication. There is also general accord that a case treated with radium should not be allowed to go into labor but should be delivered by cesarean section. There is not the same general accord in those cases apparently cured by cautery amputation, though I believe the majority of authorities would not permit a cervix, once the seat of cancer, ever to be traumatized by a subsequent labor. While cases have been safely delivered by normal labor, cesarean section is undoubtedly the best method of delivery.

I take it there would be general agreement in favor of complete hysterectomy in the first three months of pregnancy where the cancer is limited entirely to the cervix. There will likely be little objection to the statement that in the late months of pregnancy the case should

be terminated by cesarean section with immediate hysterectomy or subsequent treatment with radium and x-ray, the choice of immediate hysterectomy or subsequent radiation depending on the stage and character of the cancer.

The prime question to answer is what shall be the treatment in the cases with the cancer too far advanced for hysterectomy and the pregnancy not far enough advanced for delivery of a viable child by section. It is now generally conceded in this country, in all borderline cases of cancer of the cervix, radium application is the method of choice. In many clinics radium has supplanted operation in all cases of cancer of the cervix. When we come to consider radium in cancer of the cervix associated with pregnancy, however, we face a new and difficult problem to solve. We have to consider not only the effect of radium on the child, but also the effect of the treatment on the cancer. While some cases have been treated with radium and gone to term to be delivered of a child, in many of the cases, as in my own, the fetus has been promptly killed and abortion has resulted. Abortion is a dangerous complication even after radiation. Channels are opened up for the spread of the disease before the radium has had a chance to fully protect the woman and metastases kill as in the case just reported. On the other hand, radium may cure the cancer and if the fetus does not die, the effects on the child may be most deleterious. Much has been written on the effects of radium on the fetus in utero. The conclusions have been based on the results of animal experimentation and clinical observations in the human. Goldstein (AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY **16**: 747) has reviewed the experimental literature and compiled the bibliography. Murphy (*Surgery, Gynecology and Obstetrics*, August, 1928) reviews the clinical as well as the experimental literature and attaches a complete bibliography. Both of these splendid pieces of work were done under the direction of Dr. C. C. Norris.

CONCLUSIONS

"Irradiation of pregnant animals or human beings is a procedure extremely dangerous to the health of the offspring concerned (61.3 per cent defective), and in the case of human beings ought not be undertaken unless such existing pregnancies are to be terminated artificially prior to the period of viability of the child.

"As yet, it cannot definitely be stated that preconception maternal pelvic radium application or x-ray irradiation is or is not prejudicial to the health of subsequent child."

In drawing conclusions from the literature care should be taken to separate the cases radiated prior to pregnancy and those radiated during pregnancy. While there may be some doubt as to the effect of preconception radiation on subsequent children, there can be little

doubt as to the serious defects which may develop in the fetus as the result of radiation following conception. While our knowledge is not sufficient at present to draw definite conclusions, it is enough to cause us to elect to do either a complete hysterectomy or a cautery amputation of the cervix rather than to use radium when pregnancy complicates the cancer.

The effects on the child both in pre- and posteonception radiation is about the most important question to be solved at the present time. It is urged that every one should carefully record their experiences so that conclusions based on a study of a large series of cases can be drawn.

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A STUDY OF TWO HUNDRED AUTOPSIES MADE ON SYPHILITIC FETUSES*

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THE study of syphilis and pregnancy in the colored race, in the South, is an economic as well as a scientific obligation. In a former study published several years ago I found that, of the stillbirths and early neonatal deaths in our clinic, 45 per cent had syphilis and 12 per cent more probably had syphilis. The incidence of syphilis in this present study is 41 per cent, with a probable incidence of an additional 8 per cent. The smaller percentage in the present study is perhaps due to the fact that more early abortions were studied in this series. The organisms of syphilis were found in 61 babies. The mothers of 3 of these babies had attended the antisyphilitic prenatal clinic; 2 of these mothers had one arsenical treatment, and the other had two treatments. Every baby was examined under the roentgen ray for evidences of syphilis in the long bones. The bones were positive in 83 babies, or 41 per cent. The mothers of only 10 of these babies had attended the antisyphilitic prenatal clinic. Not one of these mothers received more than three treatments.

THE DIAGNOSIS OF SYPHILIS

A positive diagnosis of syphilis was made upon the finding of one or both of the following: the demonstration of the organisms of syphilis in the stained tissues, and the characteristic lesions of the long bones as revealed by the roentgen ray.

A probable diagnosis of syphilis was made when the maternal blood Wassermann reaction was strongly positive and the histologic changes in the mature placenta were plainly positive.

*Read by invitation.

PREMATURITY

One hundred and thirty-nine, or 69.5 per cent, of the babies were premature. Of these premature babies, 52 per cent had syphilis. Seven other premature infants probably had syphilis.

Intrauterine age was roughly estimated by the weight which was, in most cases, taken at birth. The accompanying table shows the weights, the number of fetuses in which the bone changes were positive, the organisms of syphilis found, or both. The smallest fetus in which the organisms of syphilis were found weighed one hundred grams; they were found in two that weighed two hundred grams, and in one that weighed three hundred and twenty grams.

Fetus	*Grams*
5	100- 500
6	500-1000
13	1000-1500
19	1500-2000
23	2000-2500
8	2500-3000
1	3000-3500

Fifty-seven babies were born at or about term; of these, 14 were syphilitic and 3 more probably had syphilis. There were 161 stillbirths; 39, or 19.5 per cent, were born alive.

HISTOLOGY

I have been able to find but little histologic work, either normal or abnormal, on the newborn. Maceration causes most of the tissues of value to be unfit for study. When perivascular infiltrations of small round cells have been found, the baby has been syphilitic in most cases; the absence of such lesions, however, does not exclude syphilis. Thickening of the walls of the blood vessels and an increase of connective tissue were found almost as often in the cases that did not have syphilis, as in those that had the disease. A gumma, recognizable as such, was not found in the entire series. This includes the histologic studies of the placentas. A better trained pathologist would probably have obtained a great deal more information from this work than I have, but I feel that it is safe to make a positive diagnosis of fetal syphilis from the presence of the organisms in the tissues and the frank long bone lesions. When perivascular infiltrations of small round cells and marked connective tissue proliferation are seen, one or both of these positive diagnostic evidences can be demonstrated. The converse of this statement is not true; that is, one or both of these positive diagnostic evidences can be demonstrated without the presence of perivascular infiltrations of small round cells or marked connective

tissue proliferation. Complete histologic studies were made on 61 cases, but the results were so uncertain and so variable they will not be reported at this time.

LONG BONE CHANGES

The long bone changes were positive in 83 of the 200 cases studied, a percentage of 41. The bones were positive and the organisms of syphilis were not found in 17 babies. I can explain this discrepancy only by the belief that in certain cases the organisms of syphilis do not take the silver stain. The bones were negative twice where the organisms were present. The bones were positive in 7 cases where no silver staining was done. The bones were positive and the placentas positive in 48 cases; the bones were positive and the placentas premature positive in 10 cases.

MATERNAL WASSERMANN REACTIONS

Negative reactions were obtained 108 times; 82 were positive and there were 10 mothers on whom the test was not made. Forty-three per cent of the reactions were positive. The blood Wassermanns on the mothers and the long bone lesions in the babies were both positive 55 times. The bones in the babies were positive and the maternal Wassermann tests were negative 21 times. The organisms of syphilis were found in 15 babies whose mothers had negative Wassermanns, and were found in 43 babies whose mothers had positive Wassermanns. The maternal and cord Wassermanns were positive in 5 cases. (Because of death and maceration relatively few specimens of cord blood could be obtained.) The bone lesions of syphilis were demonstrated in 6 babies whose mothers had no blood Wassermann tests. The maternal Wassermanns were negative in 5 cases in which the cord Wassermanns were positive.

CORD WASSERMANNS

Only 88 cord Wassermanns were done, yet 25 per cent of them were positive. The cord Wassermann reactions were negative on 8 babies who had syphilis, and positive on 20 babies with syphilis. The reactions were negative in 4 cases with probable syphilis. The organisms of syphilis were found in 37 babies on whom cord Wassermanns were not done. The long bone changes were positive in 56 babies where the cord Wassermanns were not done. Evidences of syphilis were seen in the bones of 5 babies whose cord Wassermanns were negative. Both cord Wassermanns and long bone changes were positive in 20 cases.

THE ORGANISMS OF SYPHILIS

The original Levaditi method of staining the organisms was used. The following tissues were routinely examined: brain, eye, thymus, lungs, kidneys, suprarenals, spleen, heart, liver, aorta, cord, uterus,

fallopian tubes, skin and, in some cases, the testicles. The tissues from 189 babies were stained. The organisms of syphilis were found in 61 cases, or 32.3 per cent. The stain was unfit for study in 11 cases.

The organisms of syphilis are a puzzle to me. Why should they be found in the placenta and not in the baby? Why should some autopsies reveal literally millions of them, and others, with positive maternal and cord Wassermanns, syphilitic bone changes and positive placentas, after prolonged search reveal none? Sometimes the organisms are long, then short, a few spirals, many spirals; some are thin, others are thick. It is probable that the thicker the connective tissue in which the organisms are embedded, the longer and thicker they are apt to be.

It would seem that the smallest organisms have been most frequently seen in macerated tissues. Fragmented organisms are often seen in macerated tissues; they appear distributed in showers. The fact that the organisms were found in 15 babies whose mothers had negative blood Wassermanns, will bear repeating.

HISTOLOGY OF THE PLACENTA

The histologic diagnosis of syphilis in a placenta at or near term is, as a rule, an easy diagnosis to make. I agree with Holland that the histologic diagnosis of syphilis in a premature placenta is exceedingly difficult. The more premature the placenta, the more difficult it is to express an opinion.

Thirty-nine per cent of the 115 placentas examined were diagnosed as positive for syphilis without comment. The diagnosis of premature positive was made on 26. Some additional data in connection with the premature placentas is as follows:

Premature positive placentas		26
Maternal Wassermann	Negative	9
	Positive	17
X-Ray Baby	Negative	16
	Positive	10

No placenta had a negative finding where spirochetes were found in the baby. When the organisms of syphilis were found in the baby, the premature placentas of doubtful histology were classified as positive. The placentas were positive and the maternal Wassermanns negative 9 times, and premature positive with negative maternal Wassermanns 7 times. The placentas were negative and the maternal Wassermanns positive 9 times. The placentas and maternal Wassermanns were both positive 37 times. The premature positive placentas and positive maternal Wassermanns agreed in 16 instances. There were 37 positive placentas where the organisms were found in the baby. The spirochetes were found in 17 babies where the placentas

were not studied. The organisms of syphilis were found in 2 placentas but prolonged search failed to show them in either baby. No placentas were negative with positive bone changes in the baby. If the placenta is mature and the histologic changes are characteristic of syphilis, there are, in almost every instance, definite evidences of bone destruction in the baby, and the organisms of syphilis can be found in the majority of cases. A syphilitic placenta with no evidences of the disease in a live baby is an indication for prolonged study and constant observation. Patchy areas that appear syphilitic should only arouse suspicion.

There were 32 cases in which the placentas, bone changes, and maternal Wassermanns were all positive, and in whom spirochetes were found in the tissues.

SOME CAUSES OF DEATH

As a matter of interest, the accompanying list gives the conditions named as having caused the deaths of some of the babies:

32	Prematurity
18	Undetermined
18	Toxemia of mother
10	Intrauterine asphyxia
6	Brain hemorrhage
4	Pneumonia
1	Atelectasis
3	Premature separation of placenta
2	Prolapse of cord
1	Pyelitis of mother
1	Prematurity of twins
1	Prematurity (one of twins)
1	Suffocation

The following conclusions may be considered axiomatic:

1. Syphilis is only transmitted to the baby by way of the placenta.
2. The lesions of the long bones as demonstrated by the roentgen ray are pathognomonic of fetal syphilis.
3. The organisms of syphilis fail to stain in a certain number of cases—probably in as many as 12 to 15 per cent.
4. A mature placenta with the histology of syphilis is rarely found without other positive evidences.
5. Even moderate antisyphilitic treatment during pregnancy will save a majority of babies.
6. Mild arsenical and mercurial treatments have no injurious effects upon pregnant women.

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